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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

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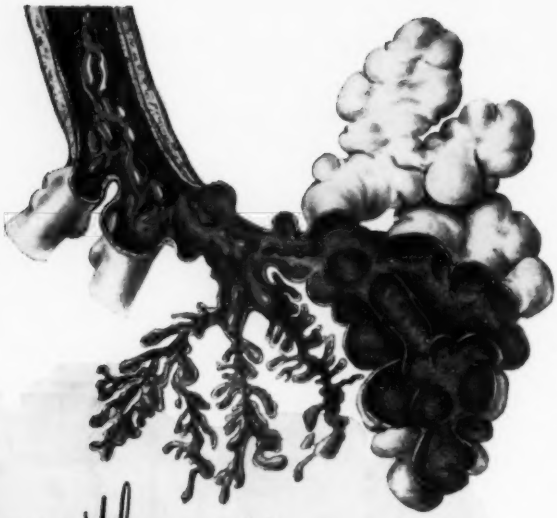

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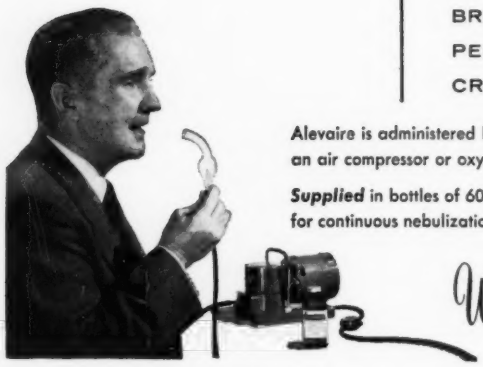

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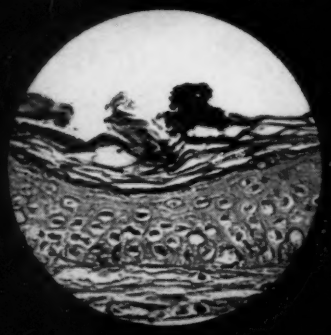

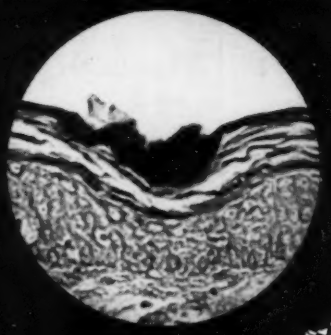

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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VOL. 37, NO. 2 FEBRUARY 1961

NEW YORK PATHOLOGICAL SOCIETY

Presented at the Meeting on December 11, 1958, at The New York Academy of Medicine

THE ANTITHESIS OF STRUCTURE AND FUNCTION IN RENAL ACTIVITY

THE PROBLEM OF ITS CORRELATION IN THE NEPHRONS AND THE KIDNEY AND AN APPROACH TOWARDS ITS RESOLUTION BY STRUCTURAL-FUNCTIONAL EQUIVALENTS*

The Twenty-Second Middleton Goldsmith Lecture

JEAN OLIVER

Distinguished Service Professor of Pathology, Emeritus, New York State University Downstate Medical Center, Brooklyn, N. Y.

As an expression of the gratitude which I feel towards my fellow members of the Society for the honor of the Middleton Goldsmith Lectureship, it may be appropriate that its subject be one which so closely concerns their daily activities. For the professional life of the pathologist is little more than a series of problems in correlation which, in their practical application, usually take some turn of the time-worn question, "Has Structure determined Function in the case before me,

* From the Renal Research Unit, The Research Department, CIBA Pharmaceutical Products, Inc., Summit, New Jersey. Manuscript received July, 1960.

and if so, in what manner?"

As I thus put the question in its classical form, two "things", that is, abstractions, concepts, postulates—call them what you will—are set in antithetical contrast with the implication that one can be "explained" in terms of the other; some sort of causal relation between the two is thereby assumed and in fact is expressed by the use of the word "determine". It is apparent at once from the logical structure of our question that we have involved ourselves not only in the most fundamental of ontological problems, the existential nature of our subjects, Structure and Function, but also in the complications of pre-Humean causality.

Now the busy pathologist need not endeavor to trace his way through the veritable epistemological morass which thus confronts him; he appreciates that it all began with Plato's curiously paradoxical suggestion that what is obviously apparent is not really real, and he recalls that the interminable disputations of the medieval Realists and Nominalists came to an uneasy equilibrium in a general acceptance of the system of Cartesian dualities. Their series is endless: Body-Soul, Matter-Mind, Mass-Energy, Structure-Function. We shall not inquire too closely into the intellectual content of these symbols, the Scholastics who were much better than we can hope to be at this sort of thing having exhausted the situation with no remarkable success; but it is disturbing to the Pathologist to be left with the implication that what he is dealing with are two things, one a more or less passive lump (Structure) that in some manner is infused with something (Function) which is more vitally "dynamic"; or as Professor Ryle describes the duality of Body-Mind, with a "clock inhabited by a ghost"[1]. Yet to such crudity of concept are we forced, if the duality is maintained, and the Pathologist is perhaps the more distressed since he is left holding the "lump" while his confrère, the Physiologist, is free to "soar on the conceptual wings" of the Dynamic.

And so we might dismiss the situation as a problem in human behaviour. Those who *like* Dualities and Antitheses, and there are many such, might be allowed to enjoy them, and those who are irked by their implications might reject them, pointing out that they arise from a certain form of our statements which, if one prefers, can be put in other terms and the dilemma so avoided.

But for the pathologist a more practical point is involved than an exercise in Linguistic Analytics; in his daily job he must accept the

duality which is passed on to him by his clinical confrères, and so he has come to make use of an intellectual gymnastic that not only solves his own dilemma, but which even at times puts him one-up in the game of the Clinico-pathological Conference. To this end, the Hegelian Dialectic, however suspect in certain politico-ideological circles, proves an effective ploy.

The *modus operandi* of this ingenious mental gambit would not concern us at this point if it had not become such a smoothly working part of our daily thinking that we are rarely aware of its operation. We do not appreciate that it is we who by *Analysis* have neatly separated the various phenomena of the disease before us into *Thesis* and *Antithesis*, assigning Structure to the pathologist and Function to the clinician. The almost schizophrenic ambivalence that thus results is clearly of our own doing and its origin is not inherent, as will become apparent later in our discussion, in "qualities" peculiar to the observational data.

But it is in the next step where the "correlation" is consummated that temptation at times arises for a bit of artful intellectual dodging; and this is not surprising, for this process of *Synthesis* of our dubious duality is at best a mysterious operation; just *how*, the skeptical Pathologist may ask, do the twain become one?

In certain situations there is at least a pragmatic answer; if we can perform the transformation on the basis of a causal connective, the result, though it might not have satisfied David Hume entirely, will be accepted as useful by the busy practitioner, whether pathologist or clinician. But in many instances this Synthesis of our structural-functional antithesis is linked by causal chains so tenuous that it is difficult to believe we have accomplished more than to restate our problem in a form which is only verbally more impressive. For example, the correlation of the structural-functional disturbances that are observed when a renal artery is obstructed by a thrombus can be accepted on a causal basis by all but the most intransigent of the modern Analytical School; but to perform the miracle of Synthesis by the suggestion that some functional disturbance, say the retention of a product usually excreted in the urine, "correlates" with a certain tubular protoplasmic disturbance, "cloudy swelling", which we have *a priori* postulated as "regressive", is not so much to stretch the "causal lines" of Russell[2, p. 453] to the point of invisibility as to twist them into the snarl of an obvious redundancy.

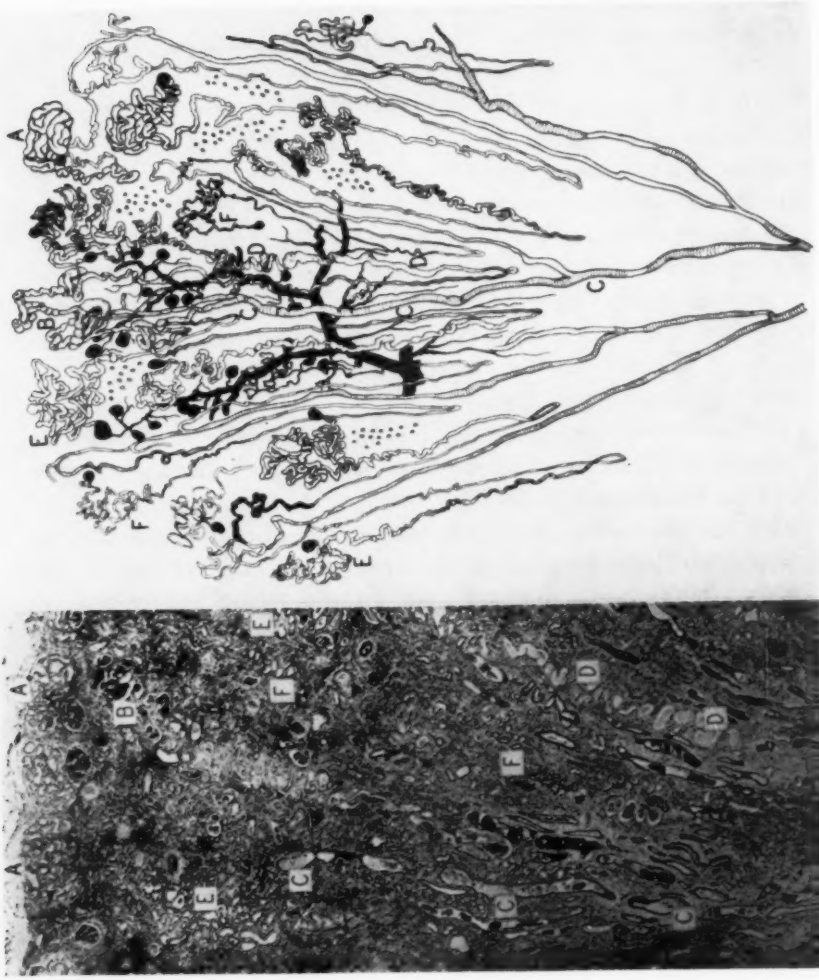

Figure 1

Granting the pragmatic value of the causally established Hegelian correlation of Structure and Function, several practical problems still remain in its application to phenomena of renal activity. The first of these is the nature or form of the data, structural and functional, on which the correlation is to be built; it is obvious if either term is wanting in validity that the operation will be spurious, and that no amount of strength on one side of the structural-functional equation can bolster the weaker member. Now the functional data of the clinician or physiologist is, in general, objective and quantitative, while the structural contribution of the pathologist is subjective and qualitative; the technician's figure of so many milligrams per cent stands, but the nature and the relative degree of tubular and glomerular involvement shifts, turns and at times even reverses itself as the protocol ascends through the staff hierarchy from Resident to Professor.

It is not clear how, in such a situation, we can do better than to settle for the best-received opinion that may be available; but these difficulties which seem inherent in the morphologist's way of looking at things are compounded by the entirely unnecessary complication that he rarely looks at and can therefore give us not even an opinion based on observation as to the state of the organs, the nephrons, the functional attributes of which constitute one-half of the correlative problem. Limiting his examination to the use of the histological section, he employs a method which indeed affords a wealth of detail concerning the nature of the processes of the renal lesion, and thereby much substance for diagnostic originality and taxonomic elaborations, but nothing in the way of information that can follow the functional changes which are occurring as glomerular filtrate passes down the tortuous conduit of the tubule to become urine. It is therefore understandable why the "Clinico-pathological Correlation", which dutifully closes the chapter on Renal Disease in the textbook, or which summarizes the autopsy protocol, so often leaves us with a bemused air of ingeniously contrived realistic unreality that might be described as worthy of Kafka.

These difficulties which stem from the disparity of the correlative data can, in part, be eliminated if the pathologist will at least *look* at the organs which are functioning. Figure 1 illustrates better than any words the difference between the two sorts of structural information which are afforded by microdissection and by the histological section.

By the former are revealed the shape of things not only in the individual nephrons, but more importantly in the now heterogeneous collocation of altered nephrons that constitute the abstraction we call an "abnormal kidney"[3]. The data are grossly oversimplified in their presentation: but may I add, since we are all so thoroughly conditioned by the subjective interpretations of the diagrams[3, p. 375] which appear in the literature of the physiological textbook and the pharmaceutical brochure, that what is shown is an assemblage of *camera lucida* tracings of the actual nephrons dissected from a specific example of renal disease. The cellular detail which would bring us closer to the boundaries where structural and functional phenomena impinge have been omitted; they have indeed in the great majority of abnormal renal situations not as yet been worked out. But the way is open for the application of all the revealing techniques of the present day, histochemical, radiographic and enzymatic procedures and electromicroscopy, if only the hands can be found to garner the harvest. Until that time comes, we can at least draw one conclusion from the oversimplified prospect that we see in my figure; and that is an appreciation of the infinite complexity of the renal lesion.

I think the clinician and also the physiologist who works with the *relative* homogeneity of the normal kidney, a situation which we shall examine later in some detail, might at least prepare himself for his attack on the problem of functional interpretation by a thoughtful moment of contemplation of Figure 1, for it shows the stark structural reality which he must face when a correlation is to be made. The present tendency is to look the other way and, since the morphologist has given him only a structural adumbration of the organ he is examining, for the functional investigator to invent a sort of meta-structure on which to base his reasoning. A "lobule" is thus described[4, p. 13] quite different from that which the morphologist finds when he takes the kidney apart, or when the "distal tubule", of which we hear so much in current literature, replaces the anatomically defined *distal convolution* along with one knows not what other well-established structural segments of the nephron. Such "structures" are clearly the result of much taking of thought and the morphologist may be gratified by the attention that is being paid to the cultivation of what he has always considered his own small garden. At times, however, he becomes uneasy lest, in some quasi-platonic sense, being led down the idealistic path of

F. H. Bradley[5], the *Appearance* he sees in his dissections may come to be considered less veridically real than the *Reality* of these ideological constructs.

Such whittling-away of the structural obstacles towards a quick and easy comprehension of renal activity reminds me that I have not mentioned one forthright resolution of the structural-functional antithesis, which, though its appeal to an audience of pathologists may be small, demands a passing note. It may be summarized as the Attitude of Transcendental Negation, for it boldly cuts the Gordian knot of our antithesis by denying that Structure has *any* existential relation to Function. Whatever the meaning of the "bizarre" configurations and patterns that the morphologist sees, they, as some idiosyncratic, perhaps aesthetic, manifestation of the Creator, may be ignored in the serious business of understanding the Kidney; for we are told: "der Fundamentalsatz nach dieser Richtung lautet: die Nieren-Funktion an sich ist in ihrer Veränderung unabhängig von der anatomischen Art der Erkrankung"[6].

Such was the prevailing climate of opinion among the clinical intelligentsia during the youth of your elder Members; against it they have fought the long, and for them, good fight along with such valiant allies, to cover a wider period, as Richard Bright and Homer Smith, on whose title pages "Morbid Anatomy" and "Structure" stand opposite and coequal with "Symptoms" and "Function". This ideological conflict is therefore worthy of a passing historical note, if not also because it may offer a psychological clue to the intransigence of an elderly Pathologist who may seem overly concerned with the King Charles head of his structural-functional antithesis.

In fact, the battle against what may fairly be considered a form of obscurantism, since it rejects one half of the evidence as irrelevant, like that for "Freedom", is never definitively won. A recent editorial[7] with de Coverley-like reasonableness seems to suggest that much may be said on both sides of the argument; that one may enjoy his structural cake but need not eat it if it appears too rich for easy digestion, or, to continue the gustatory metaphor, that the wise man will handle his Structure like strong drink, knowing when to take it and when to leave it alone. The fallacy in this seemingly temperate and certainly convenient attitude, which accepts a relation between Structure and Function until the going gets hard and the "bizarre" nephron is counted odd man out,

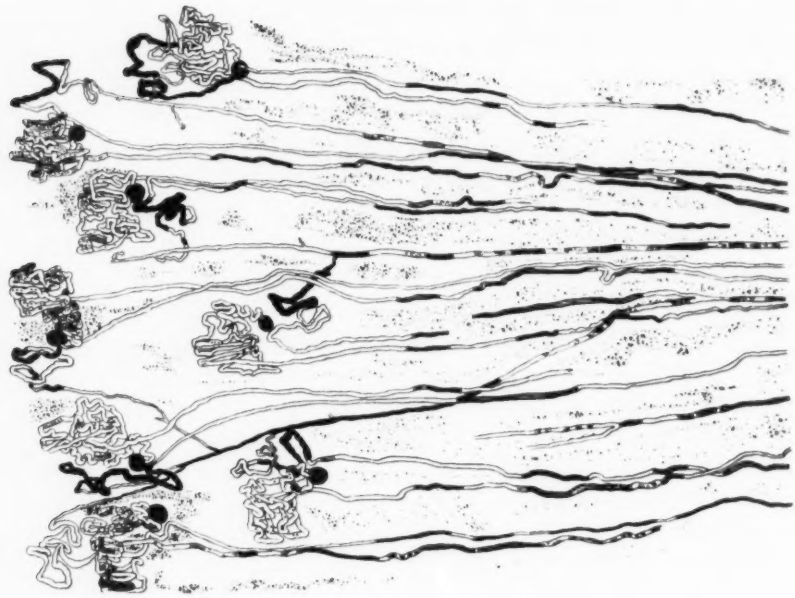

Figure 3

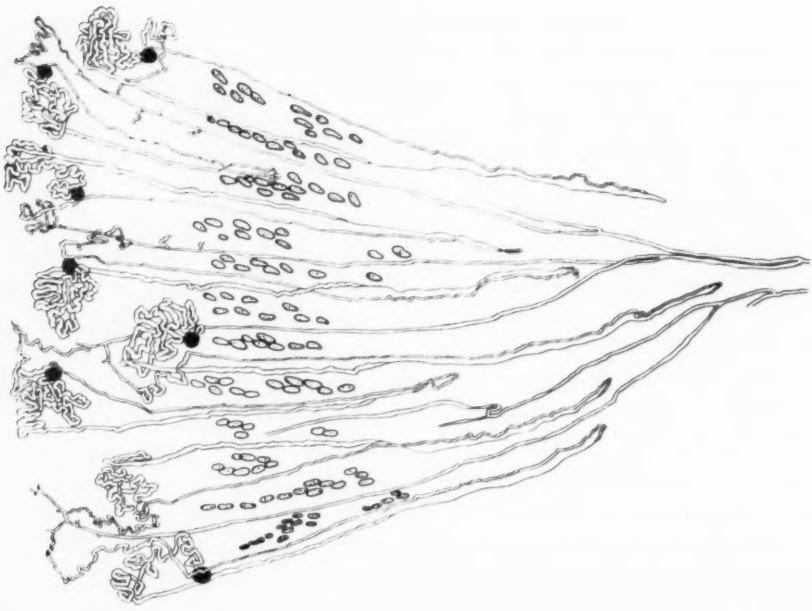

Figure 2

stems, as I shall endeavour to show, from a primary fallacy in the question it begs; that is, the assumption of the antithetical duality of Structure and Function.

Our immediate concern is not, however, with the self-searchings of the rejected Morphologist but with the meaning of structural-functional correlations to those who still believe in them; and it would seem certain that to correlate a "Structure" that has been derived hypothetically from Function, with Function as it is observed, is to indulge in a tautology which accomplishes nothing.

If the structural complexity of a chronic renal disease such as glomerulonephritis (Figure 1) seems for the present beyond our powers of exact functional interpretation, at least something can be accomplished in the much simpler situation of Acute Renal Failure, in which a kidney of normal structural configuration is damaged by a combination of ischemic and toxic insults[8]. Both the resulting functional disturbances of oliguria and diuresis can be related to the structural changes that are seen in the nephrons; the phenomena of diuresis can indeed be traced to the intracellular level, where structural alterations in the mitochondrial organelles of the tubular cells coincide with enzymatic deficiency and the failure of transport processes[9].

The renal lesion in Epidemic Hemorrhagic Fever, a special case of Acute Renal Failure[10], affords a particularly favorable example for such correlation, as here a dramatically varied clinical course proceeds, phase-like, through a diversity of functional renal disturbances which can at least tentatively be understood in terms of the concomitant changes which are seen in the nephrons. In Figures 2 and 3 are shown these structural configurations in the markedly different clinical situations of the early Hypotensive Phase and in the succeeding Phase of Oliguria. In these contrasting clinical states the relatively simple difference between the lesion of congestion and of hemorrhage in the outer *medulla* has produced contrasting changes in the nephrons that are compatible with the functional disturbances.

So far I have discussed only the practical difficulties which are inherent in the Hegelian correlation of Structure and Function as it is applied by the pathologist in his daily chore of dealing with kidneys. At the higher conceptual level more disturbing uncertainties arise when, for example, the clinician inverts the classic question, "Did Structure determine Function?", and points out that Function obviously may

determine Structure. The more thought the pathologist now gives to his answer in any given case, the less certain he becomes in which direction it should run. To return to the thrombus in the renal artery: although it would seem clear that the structural occlusion "determined" the localized ischemia, was not the origin of the structural characteristics of that thrombus, even to the configuration of its Zahn's lines, determined by the functional flow? And, entangling himself further in his philosophical analysis on a higher level of abstraction, in which he shifts his position and mixes his subjects and predicates, surely it was the absence of functional flow and the resulting anoxia rather than the structural attributes of the thrombus that produced the damage.

The usual escape from these semantic entrapments is to quote Childs' metaphor of the biological process as a river, the flow of whose waters is the dynamic flood of Functional Activity and whose banks are the static form of Morphological Structure; each, by erosion or deflection, determines the other. But this solution, it would seem to those who really dislike dualities and antitheses, is at best only a poetical way of begging the question; for, to continue Childs' analogy, it is to plunge boldly from the solid bank of Structure into the shifting Functional flood and then scramble back again to the safety of a Structural *terra firma*. The correlation thus becomes an interminable series of mental acrobatics that give much evidence of intellectual agility but little of any assured philosophical equanimity on the part of the pathologist.

Now a statement which runs in both directions, as our question seems to do, may be suspected of hiding a tautology and this suspicion leads us to look to the modern philosophers for some solution of our problem that might eliminate both the duality and its antithesis.

Professor Woodger, who devotes six chapters of his Biological Principles[11] to the resolution of various antitheses that plague the biologist, reassures us that between Structure and Function there need be none; to quote, "Far from being insoluble it is the easiest of all antitheses to overcome. A little reflexion will show that it rests simply on the separation of space and time and if this separation is not made, the antithesis between structure and function falls to the ground".[11, p. 237] From the pages which follow, it is not apparent how the biologist is to remove his problem from the realms of "space and time". Nor does the statement that "what the anatomist deals with is an *object* not an *event*" reassure him, especially as the inert concreteness of that object is em-

phasized by repeated statements that it is usually "pickled"*. In any case, we are told by another eminent philosopher that *events* have structure and therefore would seem to share the attributes of *objects*[2, p. 250].

And so the Pathologist takes his leave of the Groves of Academe, confused by resolutions of his problem that seem not only contradictory but which at best are purely verbal and undemonstrative. Everyone, as Mark Twain said of the weather, talks about the antithesis of Structure and Function, but no one *does* anything about it.

Now in one scientific area something has been done about duality and antitheses and not, to paraphrase the poets, with the "whimper" of metaphysical periphrasis but, in that "shot heard round the world", with a most demonstrative "bang". I refer to the resolution by the physicists of their fundamental duality of mass-energy by the simple statement of an equation of identity: $E = MC^2$.

To suggest that the biologists, and in the person of their not most avant-guarde examplar, the pathologist, can follow in the way of the pioneers of the present day Queen of the Sciences, may seem at first blush unlikely, but let us see how far he can go towards such a direct and forthright resolution of his duality and its antithesis.

On a former occasion I made a tentative approach to such an endeavor and in the light of its obvious failure promised to try again[12]. A very considerable amount of quantitative data, both structural and functional, is the first requisite in any such procedure, so that whatever success I may report on this second attempt is due to the aid and counsel I have received from my collaborators, Dr. Stanley Bradley and his group, who performed the functional experiments to be described, and Muriel MacDowell, who did the dissection.

Any attempt at a correlation by dimensional identity between structure and function in the area of renal activity must begin with the recognition of the fact that its solution may lie on one of a succession of observational levels[13]. From the viewpoint of renal structure we can deal with what, in the light of the revelations of electromicroscopy, has become a series of infinite regress: the kidney, the nephrons, the renal cells, the intracellular organelles such as compartments and mitochondria, and these each with their internal systems of membranes and

* This evocation of the image of the dusty corridors of the Mid-Victorian Anatomical Museum seems hardly relevant to the activity of present day morphologists, who in their daily routine follow the progress of, say, intracellular mitochondrial transformations in the living cell by means of time-lapse phase microscopy. And even when "pickled", renal biopsies taken in series during the evolution of a disease become cinematographic "frames" which denote progress in time.

"double" membranes. Membranes are not simple sheets of substance, but, as we know from Langmuir's demonstrations, spatially oriented molecules, and this structural pattern affects their qualities. Molecules, in turn, and their dynamic properties, are dependent on both their atomic content and the pattern of its configuration; so far as we can see, or indeed imagine, structural relations prevail.

From the viewpoint of renal function we may be concerned in our correlation with urine/plasma ratios and a great variety of data derived from observations which indicate the movement, i.e., the "transport" of ions or molecules from one place to another, usually across membranes. The site of these movements can be localized and their magnitude measured by a diversity of technical procedures which vary in their objectivity from the relative certainty of Richards' sampling by micropuncture to the rather lesser exactness of those recent ingenious refinements of the urologists' two-glass test which are designated as "stop-flow analyses".

Much of the difficulty, and most of the confusion, in past attempts at correlation have come, I believe, from observation on one level, or an ill-defined or even unknown level, with inference operating on another. Both the investigator of function and the morphologist are subject to this error, the latter surely with less excuse, as he should be able to see what he is doing. I must, therefore, explicitly define the observational levels with which we shall be concerned.

The renal correlation I have chosen as a test case will describe how the kidney and the nephrons handle glucose; from the structural standpoint we shall consider the spatial dimensions of two components of the *nephron*, the glomerulus, through which glucose enters the lumen of the tubule, and the proximal convolution by which it is removed from the tubule fluid. On the functional side, we shall be concerned with relations between concentrations and amounts of glucose in the blood passing to the *kidney* and those observed in the urine leaving it. No difference in observational level between kidney and nephron is here involved, for the data derived from the kidney, as will be apparent, can be reduced to the common denominator of the nephron by what has been learned through direct visual observation and quantitative measurements with the methods of micropuncture and microdissection[14]. We also know from these procedures that no other parts of the nephron are concerned in the handling of glucose.

The development of the correlation will proceed as follows: first, a general examination will be made of the situation in the normal human kidney comparing structural measurements we have recently completed with functional data derived from the previous studies of Dr. Homer Smith and his coworkers[15]. As a result of this comparison and a consideration of Dr. Smith's theoretical analysis I shall then propose certain *structural-functional equivalents*, the validity of which will be tested by their use in the quantitative description (titration) of the handling of glucose by the kidney and nephrons. Certain specific aspects of the problem which have arisen in this general survey will then be reexamined, using structural and functional measurements made on the kidney of the dog; the latter were done by Dr. Stanley Bradley's group.

THE STRUCTURAL DATA IN THE HUMAN CASE

It is commonly stated that the length of the proximal convolution in man is 15 mm., a figure based on Peter's[16] measurements of five nephrons in three individuals of unknown age and weight. Pai[17], on the other hand, measuring nine nephrons from three "young men", found a mean length of 20.1 mm. The glomerular measurements of the two investigators differ even more, being 155 μ and 300 μ respectively for average glomerular diameter. It is clear, therefore, that we start with no firm data regarding even mean values and none at all in regard to the distribution of variations in size of the renal elements.

We have measured by means of microdissection the dimensions of 104 glomeruli and their attached proximal convolutions in three young normal adults who died of acute accidents*.

First, as to the length of the proximal convolution: it is this dimension which has been mentioned most frequently as a possible determining factor in the reabsorption of sugar and has therefore been suggested as a structural correlate[15, p. 105]. It is seen in Figure 4 that, although there is some irregularity in the symmetry of the histograms of the individual cases, the mean and ranges are similar, and that consolidation of the 104 examples produces the figure of a normal frequency distribution.

But can simple length of the convolution be an adequate measure of its functional potentialities? Would not a thick, but shorter tubule contain as much or more active protoplasmic elements, such as the enzymes

* The detail of this and other technical procedures along with a fuller statement of the problems encountered and the rationale of their solution will be found in a future issue of the *Journal of Clinical Investigation* (in Press).

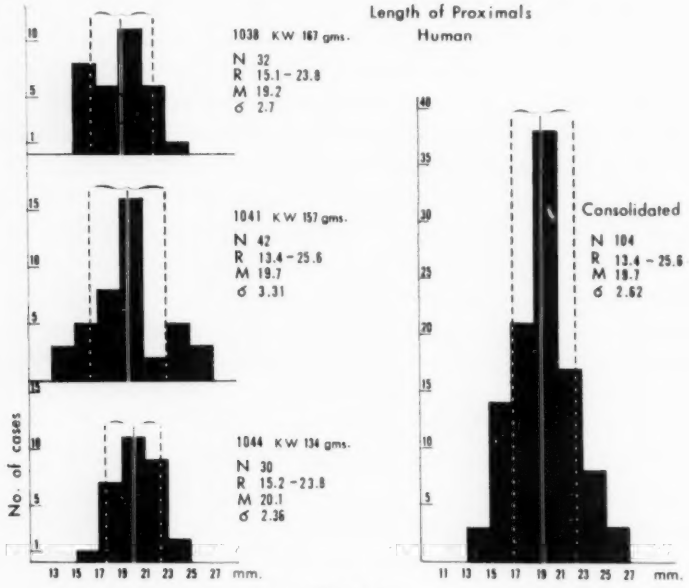

Figure 4

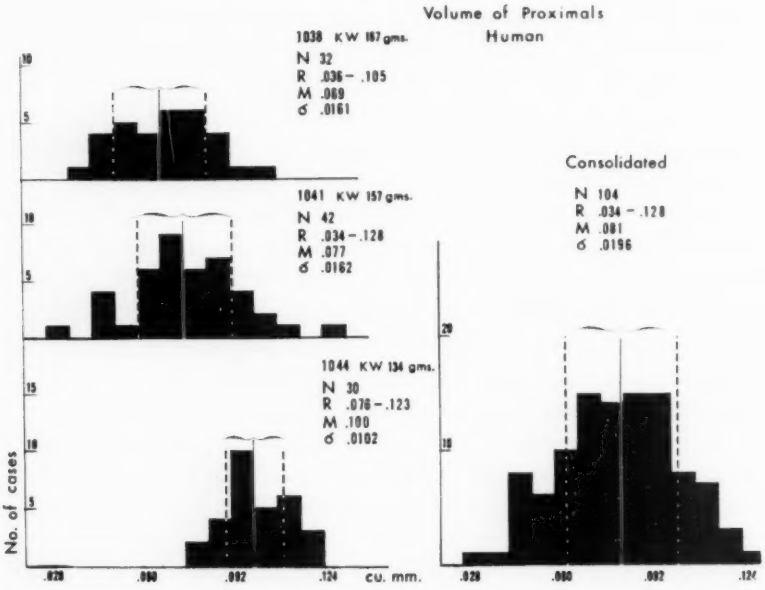

Figure 5

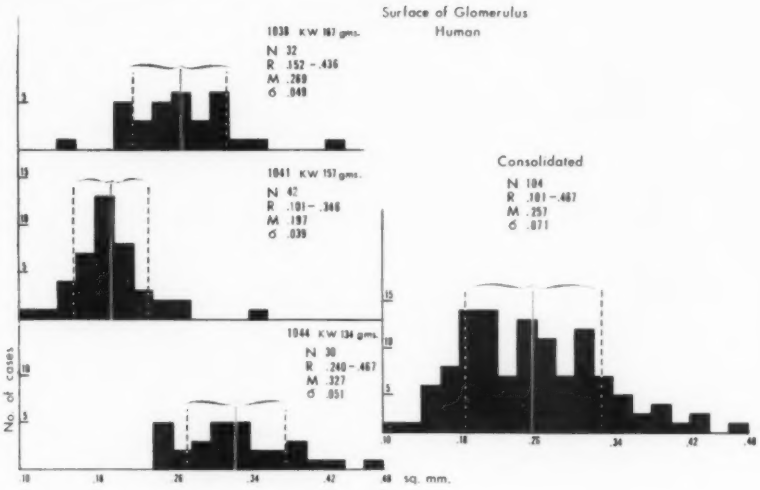

Figure 6

and substrates that are essential factors in its function? Moreover, the functional procedure with which we shall be concerned measures the degree of *saturation* of the reabsorption mechanism, and this might seem to correlate more appropriately with the mass of the tubule cells. The volumes of the same convolutions are shown in Figure 5, the average of 10 measurements of diameter in each convolution being used in the calculation. More variation in range and mean are observed between the individual cases than in the case of length of convolution, but again consolidation of the data gives a statistical distribution in the normal pattern.

In considering the dimensions of the glomerulus in the light of its function as a filter, the surface of the tuft might seem to be a factor of importance. In Figure 6 it is seen that the glomeruli attached to the regularly distributed convolutions vary considerably in this regard in the three individuals as to mean and range and that consolidation of the data produces a frequency distribution with a definite skew. On the other hand, it has been argued that the essential mechanism of filtration is determined within the tuft at the capillary surface and that this dimension, too involuted for direct measurement, would best be approximated by the volume of the mass of its blood channels[18, p. 570]. The results of calculation of the volume of the tuft made from the average of the two somewhat different glomerular diameters are seen in Figure 7

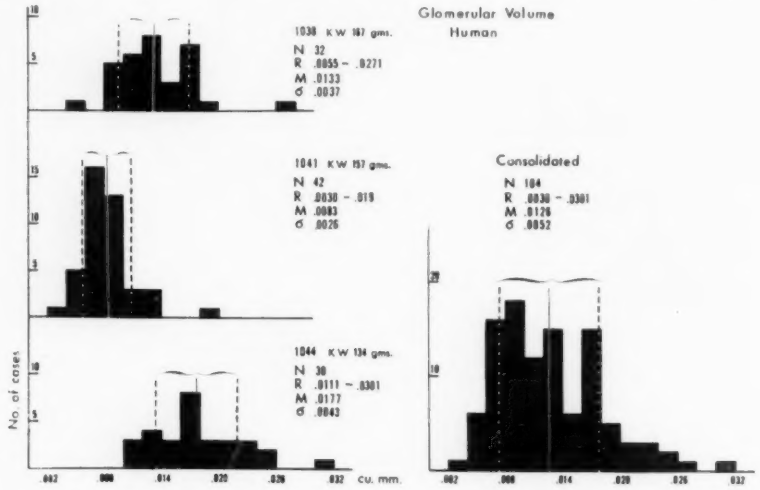

Figure 7

to give statistical patterns not unlike those observed in the comparisons of the tuft surfaces both in regard to variation in range, mean values and in distribution.

We see, therefore, that the population of nephrons in the normal human kidney shows a considerable degree of variation in structural dimensions of various sorts. We have available for correlation with function at least four different sets of these variables; surface and volume of the structures which put glucose into the nephrons, and length and volume of the elements which remove it. Since the size of the glomerulus and the proximal convolution vary in each nephron and the functional capacity of each nephron can be assumed to be the resultant of this relation, it is clear that in our use of structural dimensions for comparison with the functional data we cannot deal with the generality of mean values, but must keep intact the integrity of the organs we are examining, the nephrons, by relating each individual structural glomerular datum to its own particular tubular dimensions. In other words, our correlation must be concerned with the structural aspect of glomerulo-tubular balance in the individual *nephrons*, and only from a consideration of the totality of these individual ratios can the description of the physiological behavior of the kidney be derived.

We have already seen that the approach by inference to a decision as to which of the various dimensions of glomerulus and proximal convolution will be the most appropriate for the correlation with the functional description is uncertain in the case of both tubule and glomerulus. We therefore leave the choice of the correlates to the results of statistical analysis. The justification for this conclusion is the well-established biological principle that in a population of individuals, those who work together, grow together.

In Figure 8 the length of the proximal convolution of each nephron is plotted as abscissa against the surface of its attached glomerulus as ordinate in 104 examples from the three individuals. It is clear that there is little evidence of any structural balance between these two dimensions of glomerulus and tubule; over a range of proximal length of 13 to 24 mm., glomerular surfaces of from 0.100 to 0.460 sq. mm. are randomly scattered. Nor is the relation improved if glomerular volume is compared to tubule length as in Figure 9.

If, however, the volume of the proximal convolution is plotted against glomerular volume, a closer relation is seen (Figure 10) in that the points begin to follow the line which represents a proportional balance. When glomerular surface and proximal volume are used as the coordinates, an even closer relation is found (Figure 11). The dimensions of the smallest nephron (glomerular surface 0.100 sq. mm.—proximal volume 0.035 cu. mm.) and the third from largest (glomerular surface 0.420 sq. mm.—proximal volume 0.120 cu. mm.) both lie quite near the line of equivalent glomerulo-tubular structural balance.

It would seem, therefore, that the dimensions of glomerular surface and proximal tubule volume are the most promising structural data for correlation with the functional aspect of our problem.

Before proceeding to this correlation, we may briefly recall certain elementary features of the manner in which glucose is handled by the nephron. We know from direct observation[19] that the sugar enters the mammalian proximal convolution in the same concentration as obtains in the blood, and if this level is not greater than that which usually exists under "physiological" conditions, it has, for all practical purposes, disappeared at the mid-point of this segment of the tubule. One half of the proximal convolution is thus normally "in reserve"; this, roughly the terminal medullary portion, may therefore be considered the *structural equivalent* of what has been expressed in functional terms as

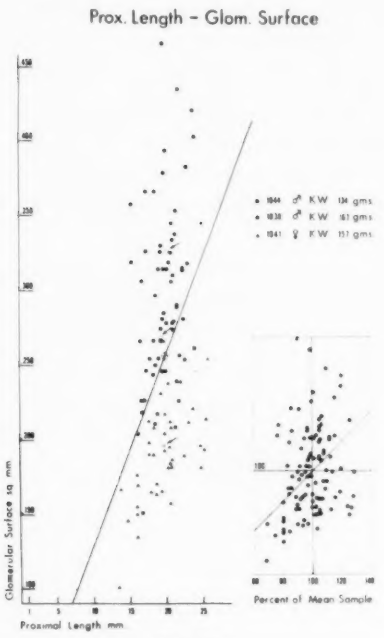

Figure 8

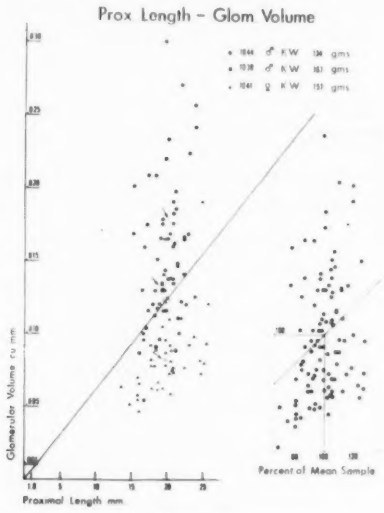

Figure 9

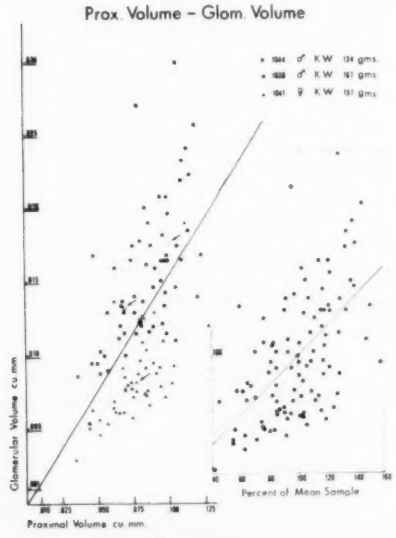

Figure 10

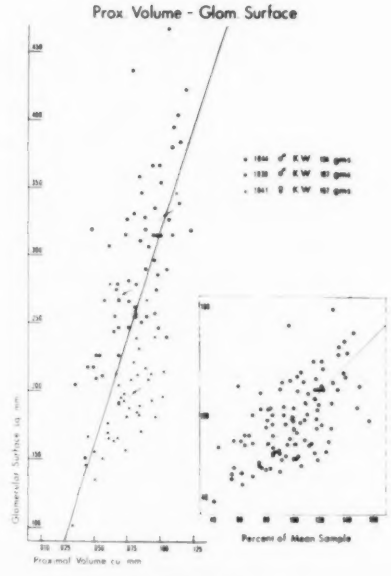

Figure 11

Figure 12

the "glucose threshold".

Since this is the first of the structural-functional equivalents that I shall propose, it is perhaps worthy of a short digression, particularly as it leads to a possible solution of a minor problem of correlation that arises at times in the Clinico-pathological Conference. It would seem from its structural definition, as Dr. Smith concludes from functional reasons[4, p. 38], that the glucose threshold cannot be identified with any fixed plasma concentration, since it depends on the activity of one half of tubular segments of varying dimensions. In theory, this threshold could be passed in two different ways, either by increasing the filtered load of glucose, as in diabetes, or by decreasing the reabsorption of it,

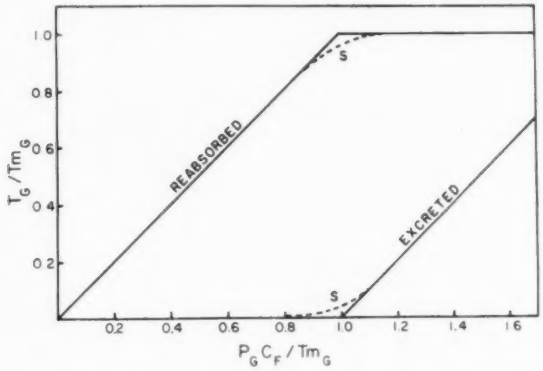

Figure 13—From Smith, H. W., *Principles of Renal Physiology*, Oxford Univ. Pr., N. Y., 1956, p. 39

as might be expected to occur with the damage to proximal convolutions that is so prominent a feature of Acute Renal Failure. As a matter of fact, the former sort of glycosuria is frequently observed clinically and the latter much less commonly; with abundant functional evidences of other forms of general tubular failure, glucose is reabsorbed even when the pathologist describes in his histological sections extensive "tubular damage". When, however, the examination is made on complete proximal convolutions with their continuity intact, as can be done only by microdissection, this paradox disappears, for a great part of the "damaged proximal", and often its physiologically most effective first portion, is found intact (Figure 12). It is therefore understandable how the "damaged nephrons" can still reabsorb a physiological load of filtered glucose with no resulting glycosuria, and also why, as will appear in more detail later, when that load is increased during the procedure of a "titration", their Tm_G is found to be reduced.

To return to the larger problem of quantitative correlation: a more detailed examination of the functional aspect of the "threshold" brings us to a critical point. If, in the presence of normal kidneys, the glucose concentration in the plasma is progressively raised, the reabsorptive mechanism is saturated, sugar appears in the urine, and after a brief period its excretion is directly proportional to the rising blood concentration; it is during the transition to this proportional glycosuria that the much discussed "splay" in the curve of excretion occurs (Figure 13).

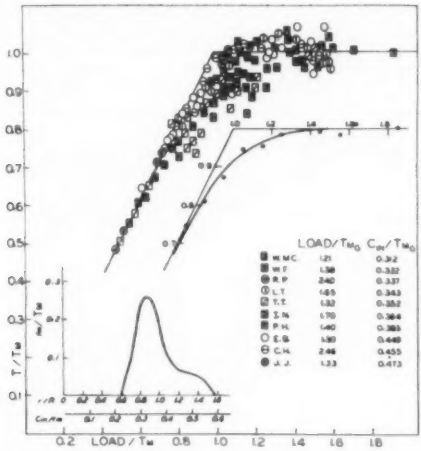

Figure 14—From Smith, H. W., *Lectures on the Kidney*, Univ. of Kansas Pr., 1943, p. 118

Two explanations have been advanced to explain its origin. It has been held that it is "overwhelmingly more likely"[20] that the splay results from a kinetic component which can be described by the Menten-Michaelis formulation of the reaction rates of the enzymatic activities responsible for the transport of glucose across the tubule wall. One theoretical analysis of this possibility has, however, found the explanation inadequate[21]. The second explanation, based on functional measurements which we shall consider later in detail, holds that the splay results from a dispersion among the nephrons of differing capabilities in filtering and reabsorbing glucose; some are quickly saturated and spill sugar early, some later, during the transition to a glycosuria proportional to the plasma level[15, p. 104 et seq.]. Why the nephrons so differ, functional evidence gives no answer, though it has been suggested that the "size" and the "shape"[22] of the structural components may be responsible. It is in answer to these speculations that our structural measurements may be helpful.

The most complete functional data for correlation are those which have been obtained by the procedure of "titration" where, on the rising concentration of plasma glucose produced by its infusion, clearances of inulin and glucose are followed past the point of tubular saturation into the range of fully established glycosuria. A detailed description of the

STRUCTURAL AND FUNCTIONAL EQUIVALENTS

Functional Measurement		*Structural Equivalent*
Rate of filtration in a particular nephron	cin	Surface of glom. tuft of a particular nephron (sq. mm.)
Glomerular filtration rate (cc/min)	Cin	Mean of all measured glom. tuft surfaces
Rate of glucose reabsorption in a particular saturated nephron (mg/min)	tm	Vol. of prox. conv. of a particular nephron (cu. mm.)
Max. value of total reabsorption in all nephrons	Tm	Mean value of all measured prox. volumes
"Glomerular Activity" (cin/tm) in a particular nephron	r	$\frac{\text{Glom. surf. (sq. mm)}}{\text{Prox. vol. (cu. mm)}}$ of a particular nephron
Total glomerular activity in both kidneys (mean value Cin/Tm)	R	Mean value of r of all measured nephrons
Relative glomerular activity of a particular category of nephrons $\frac{\text{cin/tm}}{\text{Cin/Tm}} = \frac{1}{\text{Pg Cin/Tm}}$	r/R	$\frac{\text{Glom. surf./prox. vol. of a particular nephron}}{\text{Mean value glom. surf/prox. vol. all nephrons}}$

Functional	*Definitions*	*Structural*
A group of nephrons with identical cin/tm ratios	Category of nephrons	A group of nephrons with identical glom. surf./prox. vol. ratios: determinable for particular nephrons.
Appearance of glucose in urine after saturation of all nephrons	Glucose "threshold"	Result of saturation of the reserve medullary segments of prox. conv. of all nephrons

Figure 15

procedure and a theoretical analysis of the entire physiological situation has been given by Dr. Smith and his coworkers[15, p. 104 et seq.], and I need here only call attention to certain details of definition with which we shall be particularly concerned in our correlation of its conclusions with the structural data.

In the upper curves of the graph (Figure 14) T represents the total tubular reabsorption of glucose (mg./min.) plotted against the load of filtered glucose which is calculated from the glomerular filtration rate (inulin clearance) and the plasma concentration of glucose; both are expressed as percentages of Tm, i.e., the maximum value of T. Again we see the splay of Figure 13, now inverted, at the point of inflection;

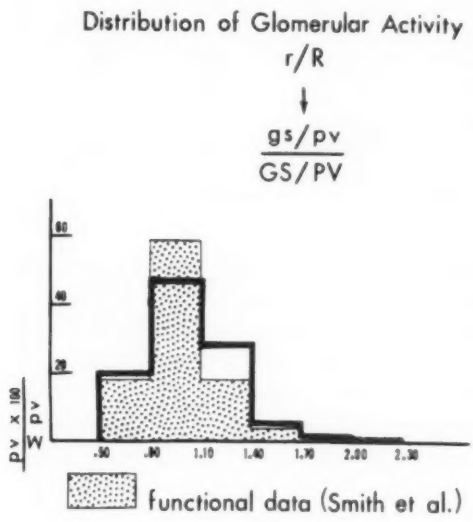

Figure 16

on the basis of the second explanation, saturation of the tubules was not coincident in all nephrons.

This dispersion in the functional capacity of the nephrons is plotted as a distribution curve in the lower half of Figure 14, in which the abscissa represents the ratio r/R with which we shall be much concerned. The value r is defined as the ratio of the inulin clearance to tm, i.e., c_{in}/tm, and has been designated by Dr. Smith[15] as "glomerular activity", since it expresses the rate of filtration (cc./min.) in the glomerulus of a particular *nephron* relative to the reabsorptive capacity in that nephron as measured by the maximal rate of glucose reabsorption in mg./min. R represents total glomerular activity of both *kidneys* and is held to be equal to the mean value of all r's. The frequency distribution curve of the ratio of r/R plotted against tm/Tm, shown in the lower part of Figure 14, is normal for the consolidated data of several human kidneys. From it the conclusion is drawn that "glomerular activity in the (human) kidney is distributed about the mean in a manner roughly conforming with a normal frequency distribution curve, the dispersion of which is such that 95 per cent of the observations fall within ± 40 per cent of the mean"[15, p. 117].

TABLE 1

	K W *gms.*	*No. Nephrons* *K W* x 7000	*MPV* *cu. mm.*	*Σpv* *cu. mm.*	*MGS* *sq. mm.*	*Σgs* *sq. mm.*
1038 ♂	335	2,345,000	.069	161,805	.269	630,805
1041 ♀	314	2,198,000	.077	169,246	.197	433,006
1044 ♂	268	1,876,000	.100	187,600	.327	613,452

Now it is possible to substitute in these manipulations of the functional data the corresponding structural measurements which we have previously found to have a statistically correlative relation and which we therefore believe may be most appropriate in the representation of functional activity; namely, glomerular surface area and volume of the proximal convolution. A summary of the various relations which we shall consider as structural-functional equivalents is shown in Figure 15.

Plotting the value of r/R with these structural equivalents in the same form as was used with the functional data, the frequency distributions of the two expressions, structural and functional, are found to be similar (Figure 16). The concluding statement of the functional investigators can therefore be amplified by a structural expression, namely, glomerular activity, whether derived directly from functional data or *expressed by relations of the structural dimensions of glomerular surfaces and volumes of the proximal convolution in the nephrons*, is distributed about the mean in such a manner that 95 per cent of the observations fall within ± 40 per cent of the mean.

The finding of a similar distribution of variation in the two different descriptions, structural and functional, suggests that we are dealing with phenomena that are comprised in one class, not two; but a more direct demonstration of the identity of Structure and Function in our case is possible.

We have previously mentioned the ambiguity of the concept of a "glucose threshold"; Dr. Smith has therefore proposed[4, p. 38] the ratio GFR/Tm_G as more pertinent in comparing the activity of individual kidneys; the mean value of this ratio in normal man is 0.37 ± 0.05 and in women 0.39 ± 0.06.

The structural dimensions of the three human kidneys are shown in Table 1. The calculation of the ratio by means of the structural-functional equivalents of Figure 15 is as follows:

If $\frac{Tm_G}{\Sigma pv} = C$, then $TmG = \Sigma pvC$

1038 ♂	$\frac{375}{161{,}805}$	0.0023		
1041 ♀	$\frac{303}{169{,}246}$		0.0018	
1044 ♂	$\frac{375}{187{,}600}$	0.0020		
		C = 0.0021	0.0018	Av. 0.0020

and if $\frac{GFR}{\Sigma gs} = C$, then $GFR = \Sigma gsC$

1038 ♂	$\frac{133}{630{,}805}$	0.00021		
1041 ♀	$\frac{117}{433{,}006}$		0.00027	
1044 ♂	$\frac{133}{613{,}452}$	0.00021		
		C = 0.00021	0.00027	Av. 0.00024

Dr. Smith's proposed ratio then becomes:

$$\frac{GFR}{Tm_G} = \frac{\Sigma\ gs \times \begin{matrix} 0.00021\ ♂ \\ 0.00027\ ♀ \end{matrix}}{\Sigma\ pv \times \begin{matrix} 0.0021\ ♂ \\ 0.0018\ ♀ \end{matrix}}$$

1038 ♂	$\frac{630{,}805 \times 0.00021}{161{,}805 \times 0.0021}$	$\frac{132.47}{339.79}$	0.38	
1041 ♀	$\frac{433{,}006 \times 0.00027}{169{,}246 \times 0.0018}$	$\frac{116.9}{304.6}$		0.38
1044 ♂	$\frac{613{,}452 \times 0.00021}{187{,}600 \times 0.0021}$	$\frac{128.82}{393.96}$	0.32	
		Av.	0.35	0.38
	Smith, observed $\frac{GFR}{Tm_G}$		0.37 ± 0.05	0.39 ± 0.06

Before our examination of the final correlation of the structural and functional measurements in the form of a complete titration curve, it is possible to test and confirm the conclusions so far drawn from measurements on human kidneys by examining the situation in the dog; here we shall have the great advantage of correlating functional and structural

CORRELATION COEFFICIENTS OF DOG NEPHRON MEASUREMENTS

	Y Glom. Surf. sq. mm.		U Glom. Vol. cu. mm.		X Prox. Length mm.		Z Prox. Volume cu. mm.	
	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
Cora N = 47	.1498	± .0155	.0055	± .0011	20.98	± 1.75	.0713	± .0080
Eleana N = 45	.1228	± .0237	.0041	± .0013	22.02	± 2.36	.0630	± .0141

	Cora D.F. 45	Eleana D.F. 43
Glom. surf/prox. vol.	rYZ .6197*	rYZ .2936**
Glom. vol/prox. vol.	rUZ .4937	rUZ .2679
Glom. surf/prox. length	rYX .2778	rYX .1701
Glom. vol/prox. length	rUX .2122	rUX .1889

*Highly significant 0.1% **Probably significant 5.0%

Figure 17

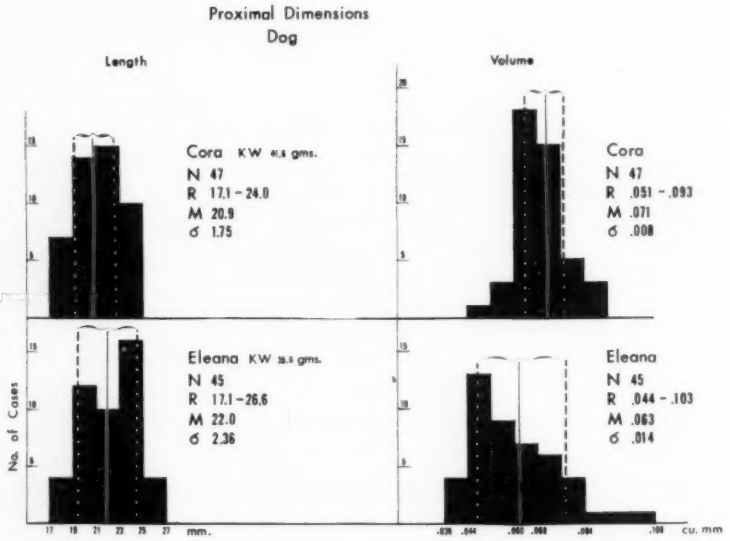

Figure 18

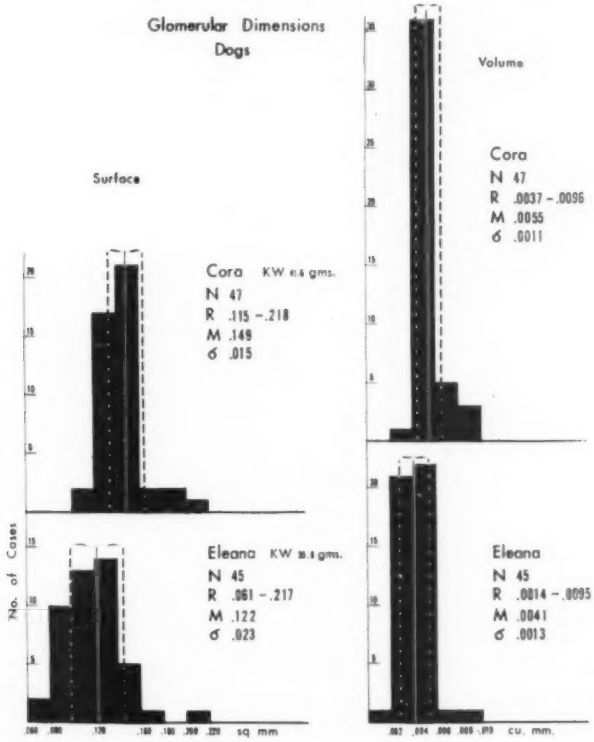

Figure 19

measurements made on the same kidney and on kidneys which vary in size. Moreover, we shall be examining an organ which is supposed to differ somewhat from that of man in that when functionally examined it appears to be more homogeneous in the population of its nephrons; as a result, the splay in the curve of glucose titration in the dog has been found to be less pronounced.

A different form of statistical evidence, confirming our previous conclusion that glomerular surface and proximal convolution volume are the proper structural measurements to use in comparison with the functional data, is seen in the calculated coefficients of correlation in two animals (Figure 17). It is at once apparent that the kidneys of dogs may vary as much as do those of men. In the more "regular" dog (Cora) the highly significant figure for the relation of glomerular surface-

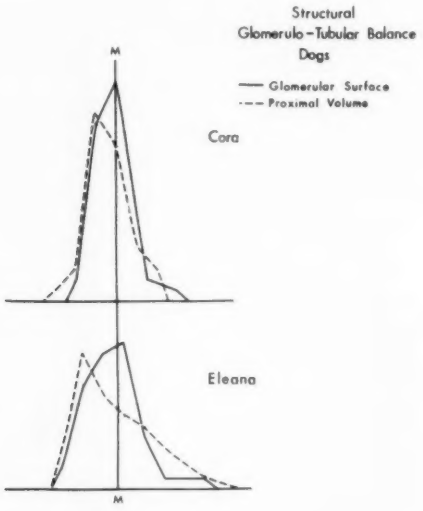

Figure 20

proximal volume is apparent; in the "irregular" kidney of the other (Eleana) the coefficient is much less significant, but it is more so for glomerular surface-proximal volume than for any comparison between the other glomerular and tubular dimensions of this animal.

The first conclusion to be drawn from an examination of histograms representing the structural dimensions (Figures 18, 19) is that the kidneys of normal dogs vary more markedly in their structural components than has been suspected from previously recorded functional examinations; indeed, one animal (Cora) shows a more homogeneous population of nephrons than is usually seen in humans; in the other (Eleana) the spread of frequency distribution is greater; moreover, the distribution of proximal convolution volume shows a decided skew. Even with these bare structural data and without recourse to the calculation of ratios, a superimposition of the means of the histograms of glomerular and proximal dimensions, now transformed into polygons, allows us to visualize, as it were, and to see how and even why tubulo-glomerular balance differs in the two dogs (Figure 20). The two curves representing glomerular and tubular dimensions of the "regular" kidney of Cora lie closely contiguous, whereas those from Eleana are separate and form two definite peaks, while the slight skew in the tubular dimen-

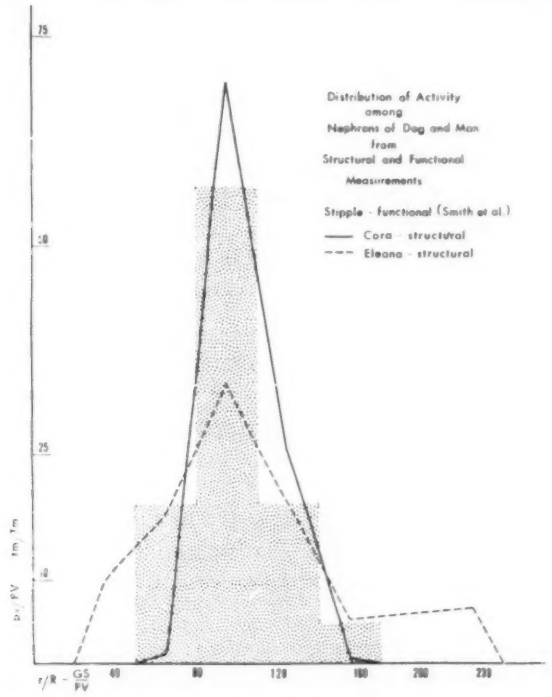

Figure 21

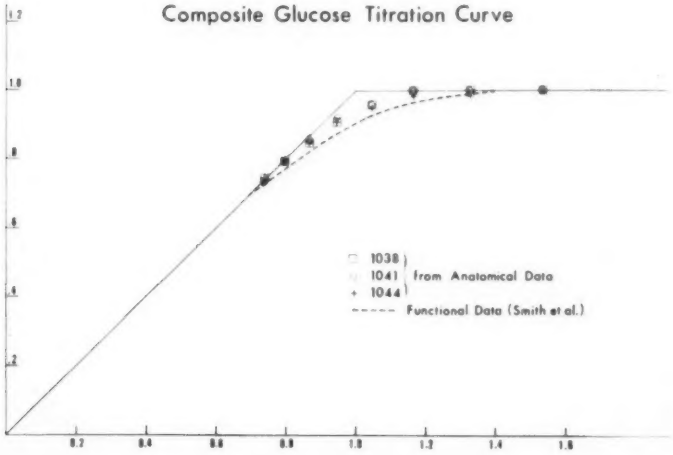

Figure 22

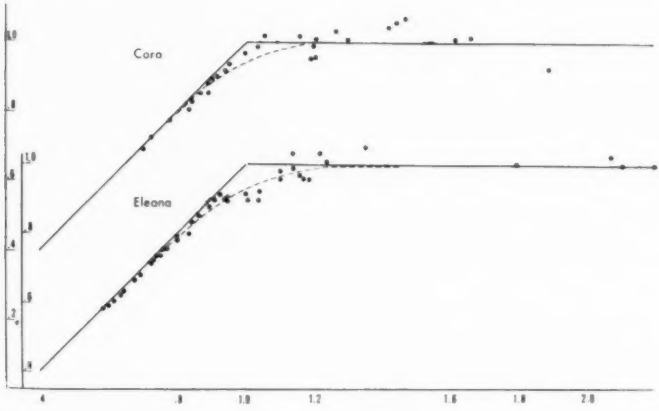

Figure 23

sions of the former is greatly exaggerated in the latter. In the light of these differences we may therefore anticipate an interesting and perhaps crucial test when we attempt our definitive correlation with function in the two animals.

Proceeding now to a comparison of the distribution of glomerular activity in the nephrons of the two dogs, the ratio r/R against tm/Tm can be calculated in the same way as was used with the structural-functional equivalents of the human kidney; when the results are compared (Figure 21) it is clear that in the case of the "regular" dog (Cora) the polygon of the frequency distribution of "glomerular activity" as it is expressed from structural data shows a closer cluster about the mean than is observed in the human kidney, the distribution of which is shown by the superimposed stippled histogram. In the case of the other dog (Eleana), however, a much wider spread is observed than is typical for man.

Various other correlative expressions might be given using the data obtained by the structural measurements in the dogs but let us now turn to the consideration of the definitive functional expression in man and the two animals as it is expressed in the conventional glucose titration curve (Figures 22, 23).

As a matter of fact, what is presented in the two figures can hardly be called "conventional" curves, for a certain artfulness has entered into their preparation. Perhaps the term "composite" would better de-

scribe them, for in the case of the human kidney (Figure 22) the dotted line with its splay is taken from Dr. Smith's previous Figure 14, where it was drawn by visual approximation to fit the points of the actual functional determinations. The points in Figure 22, however, were calculated by means of structural-functional equivalents from the anatomical dimensions; as is evident, they approximate the functional line well within the bounds of expected variability and error.

In the case of the dogs (Figure 23) I have deliberately confused matters in order to emphasize the equivalence of the functional and structural measurements; the points of the figure are the actual functional determinations of Dr. Bradley's group, whereas the dotted line is calculated from the anatomical dimensions. As can be seen, the splay in the "regular" kidneys of Cora is less than that of the human cases and fits the functional points as well as would the visual approximation of a smoothed curve. In the more "irregular" kidneys of Eleana, the splay is greater.

We thus have come to an identical quantitative description in gm.-cm.-sec. units of the handling of glucose by the nephrons and kidney by measuring either the dimensions of their Structure or the magnitude of their Function. Specifically, Tm_G, GFR and their ratio, Tm_G/GFR can be derived from either the structural components or from the movements of glucose between blood and urine; or the two sorts of measurements can be combined in an expression, the titration curve with its splay, that describes the course of the process. How, then, are we to define "the nephron" in terms that will include the unity of its structural and functional aspects?

If we depart from the assumption of a duality of its Structure as opposed to its Function, we arrive in our final mathematical expressions at an identity. Two descriptions, one of a curiously contrived physical lump and another of a "Dynamic" that in some undefinable manner informs its substance, seem not only superfluous but otiose, for to return to the analogy of Professor Ryle, the clock and its ghostly inhabitant prove to have the same dimensions and therefore presumably the same extension in space and time. Our ghost, thus taking on the attributes of the body which contains it, loses its spectral identity and the illusion of the duality that created it vanishes.

As to what remains, we must return to our earlier description of the nephron as a manifestation of phenomena occurring on a series of infinitely regressing levels of organization[13]. To the present the biologists can follow this descent into the infinite only a certain distance; in its structural aspect, the morphologist approaches with electron microscopy to the molecular level, while in its "dynamic" functional aspects, the physiologist and biochemist do somewhat better in their measurement of the movements of ions; beyond these, we must draw on the revelations of the physicists for comprehension of what we cannot as yet see and measure.

How then can the morphologist better describe the nephron than in the words of the poet of two thousand years ago, where the "atoms" within the luminal fluid in their ceaseless and varied motions ("magis adsiduo varioque exercito motu". De Rerum Nat. II, 100) "swerve" in ordered procession to give the appearance of dynamic functional activity as they pass through tubule cells which are themselves collocations of the same atoms arrested ("et quaecumque magis condenso conciliatu". De Rerum Nat. II, 100), but only for the moment, in the ever-renewing patterns of denser aggregations which we know as structural Form? And if this description leaves him with an uncomfortable feeling, as it apparently did Aristotle, who complained of the "laziness" of the Epicureans in their neglect of a more detailed analysis of the "motions" of their atoms, and he still senses a duality between the "billiard balls" and their "movement", he may, leaping 20 centuries in time, follow the philosopher Russell in his transformation of the Democritean "particle" into the Einsteinian "particle-event"; and with "events" all that remains is that something is observed to occur in a space-time relation the description of which depends on the position of the observer[23, p. 832].

If the speculative Morphologist thus moves with what may seem a suspect facility on atomic levels of conceptual abstraction, the skeptic, or should I say the practical man, will probably listen to a certain point, but eventually comes the Johnsonian reaction. For his common sense refuses to believe that the stone in the path before him is not indeed the inert clod which the worthy Doctor kicked so violently in his refutation of the Bishop's fancy that things are not what they seem to be. Had he been aware that, in the aspect of its dynamic activity, the stone was rather like a swarm of bees in its atomic configuration, the demonstration might have seemed to him not only futile but even hazardous.

But in our case it was at just such a concrete and common sense level as the stone in the path, the nephron with its glomerulus and convolution, that the duality of Structure and Function was found illusory. The testimony of the physicists and philosophers need only be accepted to encourage the morphologist to carry the analysis into realms of organization not yet open to his methods.

In a more comprehensive definition, the nephron thus becomes a locus of certain defined biological activities, a process* of "events," to use Russell's terms, which can be described from the two different viewpoints which it is convenient to call its structural and its functional aspects.

It was not in the observed, but in the observer that our refuted duality lay. And the Pathologist turns again to the physicist for illustration and quotes as once before, at a time when demonstration still eluded him[24], Schroedinger's analogy in the resolution of his similar problem, where, as he says, "in the same way Gaurisankar and Everest turn out to be the same peak seen from different valleys"[25]. Successful correlation, in compliance with the final clause of our definition of the "nephron", thus becomes a maneuver of the observer into the fortunate position where what appears to be two is seen to be one.

Now it is immediately apparent that the finding of such observation posts will not be a simple matter when one considers the series of infinite regress in levels of structural organization that I have previously described, where from "kidney" to intracellular "microsomes" we continue on, our imagination sparked by the physicists, through molecules and atoms, electrons and lesser "particles" and ultimately to the philosopher's "event". The point of correlation may lie on any step of this descent; where shall the observer pause for his comprehensive view of the unity which he seeks?

A clue towards the answer can perhaps be found in the fact that the procedure of quantitative correlation contains within itself a guiding principle for its resolution. For our basic assumption, long supported by observational verification of past experience, is that in the biological process the very origin, development and definitive growth and form of the structural components *are* functional, i.e., adaptive, adjustments to environmental change and that, as a sort of "steady state", the whole phenomenal complex is so intimately tied together as to be indivisible.

*I use the word "process" since the nephron is manifested as a multitude of events which leads to the transformation of blood into urine.

A statistical examination of the various structural data of the problem may therefore reveal some particular and pertinent relation and so mark the point of correlation.

We were fortunate in our case that the correlation point lay on a readily accessible level and that we needed to assume but four possible correlates, surface and volume of the two structural components of the process. If difficulties and complications are to be anticipated when the investigator is involved in his quantitative measurements on the level of intra-mitochondrial membranes and the movements of molecules and ions under enzymatic control, surely in these days of ever-increasing technical facility, we cannot deny its eventual accomplishment.

Having thus ejected Duality through the front door on the easily accessible level of structural-functional organization and circumspectly barred its reentrance through the subterranean corridors where the activity of the enzymologists and seekers after "fine Structure" so busily reverberate, I am aware of the host of more immediately practical questions that may be raised regarding the general applicability of what may seem an over-simplified resolution of the problem of correlation.

From what has been said it follows that successful quantitative correlation of the structural and functional aspects of any renal activity is strictly dependent on certain requirements.

First, the functional data must be based on an accurate description and localization of the activity in the nephron and on equally certain and measurable structural characteristics. The direct methods of micropuncture and microdissection have fulfilled these requirements in the case of the handling of glucose; I am not aware of any other example of renal activity for which the data have been thus firmly established.

Secondly, the measurements, structural and functional, must be made under defined standard conditions which can be regarded as representing a base line of normality if for no other reason than that the normal situation presents in the relation of its structural and functional aspects a "steady-state" which is determinable. For the abnormal situation, the difficulties of definitively measuring a "drifting" potential across a damaged membrane might be considered analogous.

These requirements would seem to preclude for the present the application of the correlative procedure to a situation where observation shows a departure from the structural relations known to be usual (normal) for undisturbed physiological activity. The effects of any

such departures cannot be predicted from the simple datum of their morphological appearances. To take perhaps the simplest case: a "thickened glomerular membrane", even if its thickness be quantitatively expressed, may be not less permeable but more so, for such is true of a freshly prepared, thick collodion membrane as compared to a thin, dried preparation. And the complexity of the possible effects of tubular cell changes staggers even the imagination.

In the *normal kidney* both the structural and functional characteristics of the *nephrons* have been directly measured[19], and it is *only* on the basis of these data and the relative homogeneity of its constituent units, that the analysis[15, p. 104 et seq.] of the situation in the *kidney* is possible by means of the over-all datum of the glucose clearance. The structural and functional measurements are found under these conditions to be equatable.

In the *abnormal kidney*, the structural *heterogeneity* of the abnormal nephrons is obviously apparent[3, 26] but direct measurement of this heterogeneity is impossible, since the variability is not only infinite, both qualitatively and quantitatively, but is involved in the infinite regress of alterations in the nephron, convolution, cell, mitochondrion . . . . The *functional* characteristics of the structurally altered individual nephrons are entirely unknown, and attempts at their determination by direct examination would be subject to the same difficulties as is the case for the structural measurements.

It would therefore seem hazardous, in the abnormal situation where the only information available concerning the structural changes is that they exist and there is none at all concerning the functional characteristics of the altered units, to attempt an analysis of the *abnormal kidney*, which is the sum of these unknowns, from the datum of a "clearance", the interpretation of which is furthermore prejudiced by demonstrable[27] alterations in its functional significance*.

*Yet it has been suggested, since the glucose clearance failed to indicate a qualitative difference (degree of splay) between various sorts of experimentally abnormal kidneys, that, whatever (undescribed) structural alterations may have been present in the nephrons, these did not affect the functional product other than to decrease its totality; the "bizarre" nephrons, it is concluded, functioned either normally or not at all[28]. This hypothesis is then extended by closely reasoned clinical argument to include all the various forms of chronic renal failure that occur in man. To the morphologist, this denial of functional significance to the multiplicity of structural alterations that are so evident to him, seems a renaissance of the Great Negation which he previously considered (p. 87) and therefore he sees no need to accept more than the negative factual findings of the experiment and to conclude again[27] that in the description and analysis of the abnormal kidney, the clearance is a poor instrument and has failed. How such a failure might come about is implicit in a subsidiary footnote of the article in question[28, p. 92]. It might be added that the use of the term "autoregulation", which seems to suggest a complexity which would make this alternative to the "Intact Nephron Hypothesis" of the text unlikely, could in the case of the glucose Tm be accomplished by a combination of the simple compensating structural changes of "atrophy" and "hypertrophy", either glomerular or tubular, and these are ever-present structural alterations in any chronic renal lesion.

In the case of the functional data, certain departures from the basic conditions of "normality" disturb the quantitative identity of the correlation in a somewhat more comprehensible manner. Cooling the kidneys lowers the Tm_G by two thirds with, it may be safely assumed, no such proportionate decrease in the volume of the proximal convolutions[29]. It would seem certain that this disturbing effect has operated on the structural-functional level of the energy-transforming system rather than on the grosser structural components; the analogy of the loss of efficiency in a steam engine with dampened fires but intact in its structural members might be appropriate; and at the level of energy transformations, as we have seen in our definition of the nephron as a series of events, it is meaningless to distinguish between Structure and Function*.

The action of phlorizin, which would completely destroy the quantitative correlation of Tm_G and Σpv observed in the normal kidney, is of especial interest as illustrating a disturbance which apparently occurs at a level of structural-functional organization remote from that which is concerned in the correlation under physiological conditions. Recent work indicates that phlorizin produces mitochondrial alterations and the evidence is "in some ways consistent with membrane theory"[30]. If any correlation were to be sought, it would seem that the data must be derived from the appropriate structural-functional level of mitochondrion and intracellular membrane.

In the face of these complexities that confront the Morphologist as he looks towards the extension of the procedures of structural-functional correlation to wider areas of renal activity, an attitude of optimistic Hope seems warranted. He admits both his factual ignorance and his technical limitations, and it is in them that he finds the reasons for anticipation of future difficulties and possible failures, rather than in metaphysical doubts as to the validity of his premises; for in the one case, where technical facility afforded the opportunity for exact quan-

*The conclusion that the antithesis of Structure and Function is meaningless affords an example of the operation of the methods of Linguistic Analytics and Logical Positivism in the clarification of at least certain metaphysical dilemmas. If one postulates *a priori* the duality, "Structure-Function", and then asks the classic question as to which is "cause" and which "effect", the answer is not that in one situation "Structure has determined Function" and in another that "Function has determined Structure" as, for example, is presumed by the analogy of Childs which we cited. A little reflection will show that in *any* specific case the argument may run in either direction; the only possible solution would be to toss the two labels in a hat and whichever were drawn would be the "right" answer. Citing the absurdity of this method of deciding between Cause and Effect might have appealed to David Hume in his elimination of the common-sense element of necessity which before his time informed the causal relation, as it illustrates that, at best, "cause" and "effect" are a description of a temporal sequence.

But if we are dealing with the *structural* and *functional* aspects of *one* thing, renal activity, the meaningless question as to whether it is "causing" itself does not arise.

titative measurement, Structure and Function were found identical in their dimensions. And in the recognition of the organ as a regressing and converging series of structural-functional levels of organization, the Duality that has "harassed . . . biological thought . . . throughout its history"[11, p. 326] vanishes in the realm of the infinitely small, where distinctions, other than that of observed events, are lost and only the "atoms and their eternal motions" remain—*sponte sua volitent aeterno percita motu* (De Rerum Nat. III, 33).

It comes as a humbling and perhaps a well-timed admonition in these days of over-proud technical achievement that at this point in the evening's entertainment, each will turn to his neighbor and say, "Is this not where we came in—2,000 years ago?"* For "in this molecular-atomic world Function seems not so much to rest on Structure" as that each is of the other's essence.

Such at least is the Faith of the Morphologist, founded, as the most eminent of authority both secular[2, p. 314] and clerical[31] commands, on the evidence of things *as yet* unseen. And if thus, with the admission of Hope and Faith (Charity surely having been implicit throughout), the Morphologist seems to stray from the narrow path of an absolute and intransigent Scientism, he now walks with his humanistic brothers supported by these most necessary of human adjuncts: he will not therefore easily be discouraged.

*In a conversation between Swinburne and Matthew Arnold, the former is reported to have boasted that the poet by pure intuition had thus anticipated by twenty centuries the scientists who depend on reason alone. Apart from this Victorian attitude, which made the scientist a dull fellow with no spark of poetic fancy (and what better example to the contrary can be cited than the imaginative arabesques which decorate renal theory), Swinburne was apparently unaware that the atomic constitution of matter had been empirically "established" by the early Atomists, who, grinding friable substance in a mortar, were never able to grind it away. With their technical facilities they could do no more; the physicists of today use the same experimental method (the disintegration of matter) and after the expenditure of infinitely greater forces, the "particles" remain. There is therefore no antithesis (the last I shall mention) between the vision of the poet and that of the scientist.

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THE ROLE OF THE FEDERAL GOVERNMENT IN PROBLEMS OF THE AGED*

The Fourth Bernard Sutro Oppenheimer Memorial Lecture

ARTHUR S. FLEMMING

Secretary of Health, Education, and Welfare

I have been asked to discuss with you the role of the Federal Government in the problems of the aging. Certainly we can say that this is a current issue as of today. I can also certainly say that it has been necessary for me to spend a considerable amount of time trying to think through my own position in connection with this particular aspect of our total operation. I am sure that it is clear to all of you that the Department of Health, Education, and Welfare has a vital interest in this particular area and has an important role to play.

Supplementing the duties that normally attach to the office of Secretary, some months ago the President established a Cabinet level interdepartmental committee to concern itself with the role of the Federal Government in the problems of the aging. He asked me as Secretary of Health, Education, and Welfare to serve as Chairman of the Federal Council on Aging. As a result, I have not only had the opportunity of viewing the problem from the standpoint of our own Department, but also of developing a bird's-eye view of the manner in which the Government as a whole approaches this problem.

I know that all of us here this evening recognize that certain problems affecting human beings at all ages are found to occur often or with greater intensity among older individuals. It is not possible to identify the age group that we have in mind. I might say, however, that the Federal Council on Aging has decided to include within the purview of its interest all who are 45 or over. That may mean that most of us here tonight are included in those who are in the process of aging.

* Presented at the Stated Meeting of The New York Academy of Medicine, April 7, 1960. Manuscript received October 13, 1960.

If we are to be really technical about it, we could include the whole population because certainly everyone is in that process, but in the economic area the problems of older people concern employment opportunities, income maintenance, costs of medical care, and something else when we recognize that the physical and emotional well-being of older people is threatened by the increased occurrence of chronic diseases and by the mounting requirements, particularly from a cost point of view, for medical care.

As we approach this problem—although I don't like to use the word "problem"—I like to think of the opportunities that confront us as a nation in the area of the aging. As we think in terms of these opportunites, we all recognize, of course, that it is fundamental in a society such as ours that each member must, first of all, seek to solve his own problems. His integrity and his dignity spring from his sense of independence and his recognition of responsibility.

Second only to his own responsibility is that of the family, the basic social unit in our culture. We all recognize, however, that the problems beyond the capacity of the individual and his family, and the problems that can properly be referred to as being related to the promotion of general welfare, become the concern of organized society. Help and services to the individual are most naturally rendered to him by the sources closest to him—sources such as the community and local State governments.

I think most of us would agree that the further removed the source of assistance, the more impersonal it becomes, and the more necessary it becomes to establish elaborate controls and methods of administration; yet at the same time we know that the time comes when, as a nation, we find it necessary to look beyond local and State governments to the Federal Government in order to make available additional resources.

This is what has taken place in the field of aging. Over the years the Federal Government has become an active participant with States and local governments and with private groups in endeavoring to take advantage of the opportunities that confront us in this area. The Federal Government has been extensively engaged and heavily involved in direct and indirect services to older people.

Considered only from the standpoint of the funds administered in various programs, this involvement on the part of the Federal Government has grown from $2.77 billion in 1950 and close to $7 billion in

1955 to an estimated total of nearly $14.6 billion in 1960. Expenditures, for example, for income maintenance have grown from $2.5 billion in 1950 and $6.5 billion in 1955 to just over $14 billion in 1960. Health and medical care expenditures on the part of the Federal Government have grown from $202 million in 1950 and $296 million in 1955 to $475 million in 1960. Housing expenditures have grown from—this is, of course, just for the aging—a million in 1950 and $7.4 million in 1955 to $48.7 million in 1960. Expenditures for employment and related programs have grown from $13.6 million in 1950 and $17.2 million in 1955 to close to $35 million in 1960.

Now some of the specific programs that have occasioned this sharp increase will come to your mind at once. For example, expenditures under the old-age, survivors, and disability insurance program have risen from about $3.27 billion in 1954 to an estimated $11.6 billion by June 30, 1961, an increase of 247 per cent in a very short period of time. Although these figures include payments to dependents and survivors, the major part goes to retired workers.

The number of beneficiaries under this program has risen from 6.5 million in 1954 to an estimated 15 million by June 30, 1961, an increase of 132 per cent.

Payments under the old-age assistance program, which are an integral part of our Federal-State public assistance operation, including medical servicing, have been liberalized to a very considerable degree over a period of the past few years. There has been a sharp increase, as this audience knows, in the funds that the Federal Government has made available for medical research. More and more of these funds are being directed to the problems of the aging.

The Hill-Burton hospital construction program has benefited persons of all ages in providing more adequate hospital and other health care facilities, but surely it has been of particular help to the aging.

Provision has now been made for a Federal Housing Administration-type of guarantee for the construction of private nursing home facilities. Here the aging will be the principal beneficiaries. But while the Federal Government is moving forward on these and other fronts in helping States, communities, and private groups to deal with the opportunities that confront our Nation as a result of the increases that are taking place in our aging population, it is aware that, as a nation, we still face many challenges in this area. In some of these instances, the

Federal Government can be of help; in other instances, the responsibility lies elsewhere. But, as we think in terms of the whole field of employment, we recognize that we still must contend with discrimination against persons because of their age.

Some States are experimenting with laws which are designed to eliminate this type of discrimination. Some have even suggested that there should be a Federal law in this area. Personally, I question that. Certainly I question it until we have had further experience with State laws and further opportunity to analyze the effects of State laws. I do recognize, however, that the Federal Government has an obligation to exercise leadership, whenever it can, in an effort to persuade employers, both public and private, that they are rendering a distinct disservice to themselves and to society by insisting on continuing discriminatory practices based on age.

Then, as we think in terms of the area of employment, we immediately think of the issue of compulsory retirement. I am sure that most of us recognize that arbitrary age requirements for retirement ignore the fact that different individuals of the same age have different capacities and desires. Personally, I feel that the arbitrary retirement age requirement is a lazy man's device for solving a difficult personnel problem. It is not easy to decide who should be retired and who should be permitted to continue to function within an organization. The line of least resistance is to use an arbitrary age requirement and to compel everyone to conform to it. I think that the Federal Government, and all of us who are interested in this particular area, should continue to point this up as an issue, and should continue to urge persons to try to resolve the issue on the basis of the facts in each individual case, instead of following, as we do so often today, the line of least resistance by falling back on an arbitrary age requirement.

In the area of housing there is no question at all but that the Federal Government has helped to stimulate progress under the programs that it inaugurated in 1956. This is not an area for which I have direct responsibility, but I am convinced that we have not yet solved that problem, that further analyses of the problem are required, and that further thinking is required as to what are the respective areas of responsibility of Federal, State, and local governments, and of private enterprise.

Certainly, there are untapped opportunities, as we think in terms

of the aging in the general field of education. Here, again, by identifying these opportunities, I am not suggesting that in every instance the Federal Government should be, let us say, providing funds, but I do think that the Federal Government should be providing leadership in this area, and there may be times when it could effect a partnership relation with States and local governments and with private educational institutions. We need to make more adequate provision for educational opportunities for continuing growth and development. We need to do a better job than we, as a nation, are doing at the present time, in terms of utilizing older persons in school and community service programs. We are just beginning to realize what our resources are along this line, and certainly there is need for general community education about the aging. Those who are experts in the educational process can make a real contribution in this direction. Educational agencies can assist employment, health, housing, welfare, and other groups with the educational aspects of their program.

We also have opportunities that we have not taken full advantage of as yet in the whole area of income maintenance. Here I am thinking in terms of the nonemployed person. I think that substantial progress has been made in the direction of strengthening the old-age, survivors, and disability insurance program. I think additional progress can be made along that line.

In the area of public assistance, I think that we could make progress if we would, somehow or other, see to it that the residence requirements are eliminated in all States, particularly where the expenditure of Federal funds is involved. There is no doubt at all but that we can stimulate the States to take fuller advantage than many of them have of the medical service benefits provided by the public assistance program.

In the area of vocational rehabilitation, this Federal-State program is placing increasing emphasis on helping the aging to realize their highest potential. More can be done in this connection.

In the whole area of health and medical care we can do more than we are doing today in applying the results of medical research to the problems of the aging.

Finally, there is this problem which seems to be in the forefront of our thinking these days, the problem of meeting the cost of medical care. It seems to me that this is not only an important issue standing

by itself, but I feel that it is an important issue because it brings to the fore all the basic, fundamental issues that we must face, as a nation, in dealing with the whole area of the aging. It is in this connection that I would like to consider with you some aspects of this specific problem.

We know that modern medical science can provide help to the elderly beyond even the dreams of a generation ago, but the individual old person's opportunities in the area of health and medical care are inseparable from his economic problems. There is, throughout our Nation, a deep-seated and growing concern over the problem of older people with lower incomes paying for modern medical care. Now we all know that very significant advances have been made in recent years in coming to grips with this problem by extending, for example, the benefits of health insurance to people 65 years of age and over. In our Department we estimate that approximately 42 per cent of the persons in this age group now have some protection against the cost of hospital care. While we do not have precise data, I think it is safe to say that approximately 6.5 million aged persons currently have some health insurance. I am thinking of those 65 and over, and the total population in that group is approximately 16 million.

Contrast this figure of 6.5 million aged persons with some type of health insurance with that for 1952, when it was estimated that only slightly more than 3 million aged persons had any coverage of this kind. As we know, Blue Cross and Blue Shield Plans have been extending their benefits and improving their coverage. Several insurance companies have aggressively entered the field to provide better protection to aged individuals. For example, Blue Cross, which now operates all over the country, has taken various steps to assure that persons aged 65 and over are offered the opportunity of obtaining protection against the cost of hospital care. While Blue Cross Plans for many years have permitted persons who have retired to continue their coverage after leaving employment, more and more such plans are providing periodically for open enrollment, when individuals of any age may subscribe for hospital coverage. Additionally, more and more Blue Cross Plans are extending the time during which they will pay hospital benefits.

While all the 68 Blue Shield Plans will continue coverage after age 65 for persons who have enrolled before that age, there are 32

plans that now offer "Senior Citizens" certificates or have no age limit for initial nongroup enrollment, and two others permit enrollment up to age 70. In addition, most other plans have similar programs for the aged, either approved or in various stages of development.

Insurance companies also have been working to make health insurance available to older people. There is considerable variation in what their policies cover and in the benefits that they provide, and it is difficult for this reason to generalize on the protection offered to the aged under insurance company policies. However, the significant fact is that more and more companies are offering group and individual coverage to the aging against the cost of nominal hospital, surgical, and in-hospital medical expenses. Additionally, some insurance companies have recently introduced or will soon present policies that will provide protection against catastrophic costs of long-term or other expensive illnesses.

In addition, more and more employers are extending the benefits of group health insurance to retired persons and their dependents. In many cases the employers are paying all or a substantial part of the cost of the group plan. I believe that we can look forward to continued progress along these lines; in fact, in a report to the Ways and Means Committee last year we stated that if this same increase in coverage of old-age, survivors, and disability insurance beneficiaries that was recorded between 1951 and 1957 continues, about 70 per cent of the aged beneficiary group will have some form of health insurance by 1965.

Taking the aged population as a whole, we estimate that 56 per cent will have coverage by 1965 and 65 per cent by 1970. Nevertheless, even though we do experience continued progress in this area, I believe we will still be left with serious problems. There will still be aged persons whose policies provide inadequate protection; also there will be aged persons who will have *no* protection but who would be willing to participate in voluntary programs if provided with policies at rates they could afford to pay.

I believe that we must approach these unsolved problems with a sense of urgency, but I also believe that we must seek and find solutions that are sound and that expedite rather than impede or undermine the progress we all desire.

As you know, one proposal, commonly referred to as the Forand

Bill, involves the imposition of an additional payroll tax under the Social Security Act in order to provide specified health service benefits on a compulsory basis. As an Administration, we do not believe that compulsory health insurance constitutes a sound approach. Our reasons briefly stated are as follows:

First, we believe that it would sharply curtail the opportunity for continued growth in the coverage and the adequacy of voluntary health insurance for the aging.

Second, we believe that it would move in the direction of freezing the pattern of health coverage of the aged in a vast uniform governmental system, thus foreclosing future opportunity for private groups to demonstrate their capacity to deal with the problem.

Third, we believe that it would include a great many persons who are not a part of the problem. The proposed solution is not pinpointed to the need.

Fourth, we believe that on the other hand it would exclude approximately 4 million of the 16 million persons 65 and over from the program because they are not eligible for social security, and in all probability they will never have the opportunity of becoming eligible for social security. This is 4 million now out of the total aged population of 16 million—25 per cent. At least 2½ million of these persons probably have annual incomes of $1,000 or less. If we ignore them, as the Forand proposal does, we are deliberately avoiding a substantial part of the total problem.

Accordingly, we have been investigating the feasibility of a program that would help accelerate rather than impede the present voluntary approach to this problem. In these studies we have been keeping in mind the following guiding principles:

First, there should be no compulsion on anyone to participate in any health insurance program.

Second, there should be no action taken by any one that would tend to stifle private initiative in the health insurance field. Anything done in this area should build on and not undermine or replace with a Federal system the excellent progress that is now being made by private effort.

Third, we believe that we should strive to strengthen and stimulate our existing private system so as to foster additional progress both in terms of scope of protection and number of persons protected.

Fourth, we believe that we should preserve and strengthen the private relationships which now characterize the rendering of health-care services.

Fifth, we believe that all aged persons should have the opportunity of participating in any program that might be developed.

Sixth and finally, we believe that there should be available to the aging, particularly in the low-income groups, protection against the severest burden of health-care cost, namely, the financially catastrophic cost of institutional care in connection with long-term and other very expensive illnesses. We believe that a gap, and a serious gap, exists at this point when looked at from the standpoint of need as against what is now actually available.

Before arriving at a final conclusion as to whether the Federal Government can devise within this framework of principles a practical program, we are exploring some issues that certainly can be fairly characterized as complex. We have, for example, been exploring the kinds and duration of health-care services that might be financed through such a program. In addition to care in general hospitals, we are considering the need for coverage of the costs of chronic care in chronic-disease hospitals, well-run nursing homes, and organized nursing services in the patient's own home. We are also exploring the feasibility of providing some protection against the costs of expensive prescribed drugs. In connection with these services we have been looking into the possibility of applying the deductible principle, which has been used widely in many insurance plans.

We have been considering methods of relating to his income the amount of money that each voluntary participant would contribute to the cost of an insurance policy. We have been analyzing possible plans under which persons in the lowest income group would make a very small contribution, and then the contribution would increase up to a given level of income. Beyond this level, the policyholder would be expected to pay the full premium cost.

We have been also exploring the question of whether State governments aided by the Federal Government could provide the difference between the amount paid by the policyholders in the low-income groups and the actual cost of the policy. In exploring this aspect of the matter, emphasis is being placed on having the States carry their fair share of the total burden.

We have also been endeavoring to identify the various factors that must be considered in getting the minimum level of protection which the States must provide in order to qualify for Federal matching funds. In exploring this question, we are keeping in mind the fact that the States would be authorized to contract with private groups for the insurance.

Finally, we are also considering the impact of any plan on the quality and availability of health services. We have not reached a conclusion as to the best manner in which to deal with these basic issues that I have identified, but in an effort to arrive at sound conclusions we are right now in the process of consulting not only with the experts in government, but also with outside experts in groups, and with State officials. I expect to complete these consultations within the next two weeks. I will then move at once to develop a specific proposal for consideration within the executive branch. So much for this specific issue!

I believe that society is giving increasing recognition to the conviction that we have an obligation not only to help children, youth, and young adults but also our aging population to realize their highest potential. This increasing recognition, it seems to me, is reflected in the passage of the law at the last session of the Congress calling for a White House Conference on Aging in January 1961.

We are now developing the plans for this conference. It will be a citizens' conference in the fullest and best sense of the term. The States are now in the process of holding grass roots conferences preparatory to the National Conference in January of next year. As these local conferences are held and as we look forward to the National Conference, I hope that in our thinking we will emphasize these points. We do need more facts than we have at the present time in this total area. I hope we shall emphasize the desirability of not trying to resolve these issues by the use of meaningless labels and slogans, but that we shall make an honest effort to come to grips with the basic issues and to think our way through to sound conclusions.

I believe that, as a nation, we are moving in the right direction. I think that in the years that lie immediately ahead, the aging will have increasing opportunities to realize their highest potential. I believe that all of us have an obligation to do everything we can to help achieve such an objective.

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

Presented at the Meeting on May 12, 1960, at The New York Academy of Medicine

RESIDENTS' MEETING

*Staining Properties of Russell Bodies in Plasmocytes and Crystals in a Lympho-plasmocyte in Comparison with Amyloids**

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(Sponsor: Alfred Angrist)

This study was made to characterize intracytoplasmic crystals in a lympho-plasmocytoid cell found in bone marrow, lymph nodes and peripheral blood in a case of an unusual lymphomatous disease**. The patient was a 60 year old woman with an obscure progressive wasting disease characterized by generalized lymphadenopathy, moderate hepatosplenomegaly and a neuromuscular disorder. She also had a duodenal ulcer and hyperthyroidism.

A biopsy of a lymph node made in 1956 showed the pattern of a lymphoma, with proliferation of lymphocytoid cells and mononuclear reticulum cells. Many crystal cells were present. The review of another biopsy removed in 1951 showed massive proliferation of epithelioid cells resembling a sarcoid reaction and some of the crystal cells, as well as eosinophils.

Various staining methods were applied to formalin-fixed paraffin sections. Tissues containing plasmocytes with Russell bodies and blocks exhibiting "primary," "secondary" and senile cardiac amyloids were used for comparison with lymph nodes containing crystal cells.

The apparent isoelectric points of the crystals, Russell bodies and amyloids were determined by the method of Singer and Morrison[1]. Sections were stained overnight in aqueous solutions of eosin (10^{-4}M) or methylene blue (2×10^{-4}M) at intervals of about one pH unit over the range of pH 3.0 to 9.5. The cross-over zone of the curves for basophilia and acidophilia was taken as the isoelectric point.

Crystals and Russell bodies in different cells exhibited an isoelectric range, pH 6.0 to 7.5. This is the range exhibited by human gamma globulin[2]. A sample of Fraction II (Mann Research Laboratory), fixed in formalin and sectioned in paraffin, gave the same range. Such a result is entirely compatible with the accumulated evidence for the production of gamma globulin by plasmocytes[3]. Apparently the crystals present in the lymphoplasmocyte described consisted of the same or a closely-related protein, in a different physical state.

By contrast, all specimens of amyloid studied exhibited a fairly sharp isoelectric

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** This was a patient at the Mt. Sinai Hospital, New York, admitted July, 1956. A description of the case is being prepared by A.F.G.

point, at about pH 5.0. The plasma proteins having comparable isoelectric points are the alpha and beta$_1$ globulins[2] and associated mucopolysaccharides. In extraction studies it has been shown that amyloids migrate electrophoretically like such globulins[4]. Furthermore, there is frequently an elevated alpha (or occasionally beta) globulin fraction in the serum of patients with amyloidosis. These observations lend support to the concept that tissue amyloid may be formed by excessive amounts of circulating globulins and mucopolysaccharides that deposit locally.

Additional staining methods were applied. All of the objects were PAS-positive. This property is compatible with the known carbohydrate content of the various plasma globulins mentioned, as well as of the mucopolysaccharides associated with globulins in amyloid. The amyloids stained positively by the Congo red and crystal violet methods. The Russell bodies and crystals did not. Formalin-fixed smears or frozen sections stained with either Sudan black B or oil red O showed no dye uptake by either Russell bodies or crystals. Yet both objects stained with the Baker acid-hematin method, even after pyridine extraction, as did gamma globulin. Although these results suggest that stainability is not attributable to a phosphatide, no possible cause is known.

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DISCUSSION

NORMAN S. COOPER: I should like to ask Dr. Goldberg whether he tested serum albumin for its isoelectric range by this same technique, and what range it fell in.

ARTHUR F. GOLDBERG: We never tested serum albumin.

CHANDLER A. STETSON, JR.: I should like to ask whether the patient who had these cells containing crystals had a cryoglobulin, or other abnormality of plasma proteins.

ARTHUR F. GOLDBERG: We did not test for cryoglobulins at that time. The patient had an abnormal electrophoretic pattern. A sharp peak was present in the gamma globulin range, but the total amount of gamma globulin was not elevated.

Localization with Fluorescent Antibodies of Complement Fixed in Altered Glomeruli

PETER M. BURKHOLDER

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(Sponsor: John G. Kidd)

With the use of immunohistologic techniques it is possible to demonstrate rabbit antibody globulin in the glomeruli of rats injected with rabbit anti-rat kidney serum[1]. Specific apple-green fluorescence is emitted from the glomerular capillary basement membranes, the sites of supposed *in vivo* localization of anti-kidney antibody that *in vitro* take up the labeled anti-rabbit globulin. Lange demonstrated that serum lost its hemolytic complement when perfused through kidneys previously exposed to nephrotoxic serum[2]. He concluded that complement was fixed in the tissue by antibody-antigen aggregates. Immunohistologic demonstration of complement fixed in tissues at sites of antibody globulin localization would provide more conclusive evidence of specific antibody-antigen aggregation and evidence of complement fixation to these aggregates.

Immune serum against guinea pig, human, or rat complement can be produced by the injection of rabbits with a special immune aggregate (SAC') composed of sensitized sheep red cell stromata (SA) exposed to complement (C')[3]. This immune serum, when absorbed with a sufficient quantity of sensitized stromata (SA), agglutinates specifically sensitized cells exposed to fresh complement (EAC'), and does not agglutinate sensitized cells exposed to complement inactivated by heat or a chelating agent. Precipitins in this absorbed anti-complement serum are also demonstrable against fresh serum (C') by capillary and agar gel diffusion methods. The immune serum when conjugated with fluorescein isothiocyanate will also coat presensitized cells (EAC').

Sections of kidneys from rats that were injected with rabbit anti-rat kidney serum 15 minutes, 4 hours, and 10 days prior to sacrifice have been exposed to guinea pig serum. It has been shown that guinea pig complement is fixed in the same glomerular sites at which nephrotoxic rabbit globulin is localized. The cut sections of kidney are first exposed to fresh guinea pig serum diluted 1/30, then rinsed and finally exposed to anti-guinea pig complement immune serum conjugated with fluorescein isothiocyanate. Specific apple green fluorescence is emitted from the glomerular capillary membranes[4]. No fluorescence is emitted by kidney sections in the following control situations: 1) sections from normal rats or sections from rats injected with normal rabbit serum, exposed first to complement and then to the conjugated anti-complement serum; 2) nephrotoxic kidney sections exposed first to heated or chelated complement and then to conjugated anti-complement serum; 3) nephrotoxic kidney sections exposed to anti-complement serum alone; and 4) sections exposed to guinea pig complement, then to non-conjugated anti-guinea pig complement serum, and finally to conjugated anti-guinea pig complement, the findings indicating that non-conjugated antibodies have blocked the uptake of conjugated anti-complement antibodies.

It is possible to demonstrate the *in vivo* fixation of rat complement in experimental nephrotoxic nephritis, using these same techniques. The nature of the mechanisms involved in the action of rat complement and other rat serum components in nephrotoxic nephritis is subject to variable interpretations and is the object of studies now in progress. Application of the principles and methods utilized in this study is also being made in search for complement fixed in lesions of tissue obtained at biopsy and postmortem in humans with diseases that may involve pathological immune processes.

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DISCUSSION

JOHN G. KIDD: Dr. Murphy, I believe, is in the audience. Does he have any comments to make on this work?

GEORGE E. MURPHY: I believe the evidence, here presented, that guinea pig complement is fixed in glomeruli in rats injected with nephrotoxic serum speaks for itself.

JOHN G. KIDD: I should like to ask Dr. Burkholder whether he can distinguish between human antibody globulin and human complement in the kidney of a person with naturally occurring glomerulonephritis.

PETER M. BURKHOLDER: That is a very good question that can also be applied to the problem of distinguishing between rat globulin and rat complement fixed in the glomeruli of rats with nephrotoxic nephritis. In the course of experimental nephritis, rat globulin, as well as rat complement, is probably localized at the glomerular sites of rabbit anti-rat kidney globulin in aggregation with glomerular antigen. The problem then is to distinguish between fixed rat complement and fixed rat globulin, since complement and globulin are antigenically related, that is, they have cross-reacting antigenic determinants. Studies utilizing coated red cells and hemagglutination technique show that anti-globulin agglutinates cells coated with complement as well as cells coated with globulin, and anti-complement agglutinates cells coated with globulin as well as cells coated with complement. When one examines kidney sections from humans with glomerulonephritis, it is to be expected that anti-complement immune serum which agglutinates cells coated with human globulin will, when conjugated with fluorescein isothiocyanate, localize in sites of human globulin as well as in the sites of human complement in the tissues. Presumably, these two serum components would localize at the same sites. Because of this problem of cross reaction of anti-complement with globulin in the demonstration of homologous complement fixed *in vivo*, we at present utilize fixation of heterologous complement, as classically done in complement fixation *in vitro*, for the demonstration of antibody-antigen aggregates in the tissues.

JOHN G. KIDD: How different are your anti-complement and anti-globulin serums?

PETER M. BURKHOLDER: The titers of agglutinins in the cross reactions are generally considerably lower than the titers of specific agglutinins. Anti-guinea pig complement, for instance, has a titer of agglutinins against cells coated with guinea pig complement of some eight times that of the titer of agglutinins against cells coated with guinea pig globulin. Anti-guinea pig globulin, however, agglutinates cells coated with guinea pig globulin and cells coated with guinea pig complement in about the same titer. The same is, in general, true with immune serum against human complement. Though the titer of specific antibodies against human complement is higher in anti-human complement immune serum than the titer of antibodies against human globulin, it is still impossible, from a practical standpoint, to obtain an immune serum against complement that does not possess any antibodies against other serum globulins.

STEPHEN S. STERNBERG: I think this question is a little bit beside the point, but will you tell us the mechanism of action of the chelating agent? How does this inactivate the complement?

PETER M. BURKHOLDER: EDTA was the chelating agent used in our experiments. Its mechanism of action is the binding of divalent cations, such as calcium and

magnesium, that are required for the action of complement to immune aggregates. The components of complement fix or act upon sensitized cells in the sequence of C'1, C'4, C'2, and C'3. Calcium is required for the fixation of the first component of complement and magnesium for the action of the second component. By removing these divalent cations one prevents the action of complement upon the immune aggregate.

HELEN WENDLER DEANE: I wondered why you stated that these antigens or antibodies, or both, were in the basement membrane. It looked suspiciously to me as though they might be in Bowman's epithelium rather than in the basement membrane.

PETER M. BURKHOLDER: The sections are not as thin as we would like. Our microtome is set to cut sections at 2.5 microns and occasionally it delivers sections up to 5 microns in thickness. Thick sections are sometimes difficult to interpret with the resolution obtained in fluorescence microscopy. Thin, delicate structures are thickened and blurred or appear to be encroached upon by brightly fluorescing neighboring structures. We observe fluorescence to occur at the site of the glomerular capillary basement membrane. The localization may be to one side or the other of the membrane, but in general it follows the contour of the membrane, so that in the glomeruli of the rats a delicate thin fluorescent membrane is observed. In studying some sections of human kidney exposed to fluorescein-conjugated sera, I often see a globular pattern of fluorescence that appears to involve thickened basement membrane, but which also appears focally to involve structures contiguous with the glomerular basement membrane. I think a great deal of the evidence indicates that uptake of fluorescent antibodies occurs at the site of the glomerular basement membrane.

HELEN WENDLER DEANE: Dr. Marilyn Farquhar has demonstrated that protein droplets are taken up by the podocytes and this may very well be similar.

PETER M. BURKHOLDER: Yes, and Vasquez and Dixon in correlating findings of fluorescence microscopy with electron microscopy have demonstrated globules of material along the basement membranes of the glomerulus that they interpret to have the properties of globulin. Of course their model in this case is a different one, namely, nephritis produced with foreign serum.

SEYMOUR COHEN: What happens when you try to absorb your anti-complement with gamma globulin?

PETER M. BURKHOLDER: In some of our studies anti-guinea pig complement serum did react positively with nephrotoxic rat kidney sections that had not been exposed to guinea pig complement. This is interpreted as a cross reaction of anti-guinea pig complement with rat complement. It is possible to obviate this cross reaction by absorbing the conjugated anti-guinea pig complement with serum homologous to the animal whose tissues are being examined. With reference to your proposal of absorbing anti-human complement with human globulin or anti-rat complement with rat globulin, I feel that most of the antibodies against complement would be lost. Apparently some of the components of complement can be isolated electrophoretically in the slower moving globulin fractions and would therefore probably be present in the globulin fraction used for the absorption. Because of this, and because of the antigenic similarities of complement and globulin, absorption of anti-complement with globulin would probably deprive the immune serum of the antibodies against complement.

Accelerated Reactivity to Bacterial Endotoxins

LEUNG LEE

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(Sponsor: Chandler A. Stetson, Jr.)

Skin tests with bacterial endotoxins in normal rabbits ordinarily produce delayed inflammatory reactions which are not grossly visible for several hours and are fully developed only after a day or more. Recent chance observations indicate that rabbits with prior exposure to endotoxins show a profound modification in cutaneous reactivity to subsequent skin tests with endotoxins. The inflammatory reactions evoked were no longer delayed and mild but accelerated and intense. These Arthus-like lesions were clearly visible within an hour and well developed by six hours after skin testing. The mechanism for the accelerated response appeared uniquely different from that of the classic Arthus reaction, since only one parenteral injection of endotoxin and a latency of only one day were required for the establishment of this modified reactivity. It was found that skin tests could elicit accelerated reactions as early as 16 hours and as late as 26 days after a modifying injection of endotoxin. However, skin tests with endotoxins on the second and third days after modification consistently elicited the strongest accelerated reactions. Serum from such animals was able to transfer passively the capacity to exhibit these accelerated responses. Like other endotoxin-induced phenomena, accelerated reactivity was also found to be cross-reactive, that is, one endotoxin could modify the cutaneous reactivity to other endotoxins.

The character of the accelerated lesion together with its capacity to be passively transferred suggest that this Arthus-like reaction may be mediated by circulating antibody produced in response to the modifying injection of endotoxin. However, precipitating antibodies against endotoxins were not found before the first week following stimulation, and moreover, they were serologically specific for the immunizing endotoxin. On the other hand, the antibody implicated in accelerated reactivity should exhibit cross reactions, appear within 24 hours and reach maximal titer two to three days after stimulation. Using the sensitive modified sheep erythrocyte hemolysis test as developed by Neter, an antibody with such qualitative characteristics was demonstrated. Preliminary attempts to correlate the intensity of the accelerated cutaneous reaction with the titer of cross-reacting antibody in individual animals were encouraging, but consistent results were made difficult by the lack of accurate quantitative expressions of skin reactivity and antibody levels. The significance of these findings and their implications in the Shwartzman phenomena and other effects produced by endotoxins were discussed.

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DISCUSSION

CHANDLER A. STETSON, Jr.: More people have injected more different endotoxins into more rabbits than one can possibly imagine, and I think Dr. Lee deserves a great deal of credit for his patience and perseverance in going over the old ground and in looking every hour at the skin reactions in these rabbits. A lot of the previous work on endotoxins has been phenomenological, and in this particular problem much more analytic work is needed. I think Dr. Lee should be commended for the way he has carried the analysis so far.

One point which has probably occurred to some is that the toxic portion of various endotoxin molecules may be very much the same, whatever the source, and serologic specificity may depend on the somatic polysaccharide, while the cross reactions described by Dr. Lee may be due to antigenicity of the toxic portion of the molecule.

JOHN G. KIDD: The cross-reacting antibody in the one experiment you showed persisted at the same titer throughout the period of observation. Did this antibody fall off in any of your experiments in the way the accelerated response regularly fell off?

LEUNG LEE: In other experiments fluctuations and declines in the cross-reacting antibody titer were observed with the passage of time.

IRA GREEN: At the site of the initial reaction was another reaction seen? After three or four days is there a flare at the first site?

LEUNG LEE: No.

IRA GREEN: Can you possibly relate the accelerated local phenomena to what happens in the generalized Shwartzman phenomenon?

LEUNG LEE: It is too early to relate in specific terms the accelerated reactivity in skin to other endotoxin-induced phenomena. However, the occurrence of an early non-specific immune response to endotoxins may suggest new lines of investigation in the Shwartzman reaction and other effects produced by endotoxins.

Gastro-Duodenal Metastases from Breast Cancer: An Adrenal Steroid Induced Phenomenon?

WILLIAM H. HARTMANN AND PAUL SHERLOCK

Departments of Pathology and Medicine, Sloan-Kettering Institute for Cancer Research, New York (Sponsor, F. W. Foote, Jr.)

In the past, metastases to the gastric and duodenal mucosa from breast cancer have been considered a curiosity. Recently, however, such metastases have not only become relatively frequent but also have been a source of clinical bleeding. In 1958, for example, such metastases were seen in 12 patients, 18 per cent of patients with breast cancer who came to autopsy.

Analysis of these cases indicated that the presence of this clinically manifest and sometimes fatal complication was correlated with adrenal cortical steroid therapy. The patient with carcinoma of the breast receiving adrenal steroids, who develops the signs of a bleeding ulcer, has an even chance that there will be breast carcinoma at the site of ulceration.

DISCUSSION

ARTHUR F. GOLDBERG: Were these patients receiving testosterone during the same period that they were receiving adrenal steroids?

WILLIAM H. HARTMANN: When we investigated the possible correlation to steroids we also investigated the correlation to practically every other phenomenon we could think of, and there was none. Some patients were receiving testosterone, and some were not.

IRA GREEN: Was the general degree of metastasis the same in patients who had gastro-duodenal involvement as compared to the group of non-steroid patients? In other words, did the steroid seem to cause metastases in other areas?

WILLIAM H. HARTMANN: As you may or may not know, there are reports in the literature purporting to show an increased involvement of the spleen in people who are on steroids, and our experience is the same. In our series, statistical studies of involvement, such as of the gastro-duodenal mucosa and spleen, show it is greater in those receiving adrenal steroids than in those who are not.

JOHN G. KIDD: Was there a difference in metastasis to the myocardium in the two series?

WILLIAM H. HARTMAN: I cannot answer that at present. We are now in the process of analyzing the data and slides relative to the difference in metastases in all organs.

Dystocia Due to Fetal Ascites
Report of a Case with Congenital Malformations of Liver and Lung

YUUJI SHINOHARA AND MASAKO SEKI

Lebanon Hospital, New York (Sponsor, Joseph C. Ehrlich)

Dystocia due to fetal ascites is extremely rare; paracentesis of the fetal abdomen may be necessary to complete delivery[1]. Fetal ascites, characterized by the accumulation of fluid in the peritoneal cavity during intrauterine life, must be distinguished from other forms of fluid accumulation in the fetal abdomen, such as distended urinary bladder, cysts, cystic kidneys, hydrops, and others[2]. Congenital abnormalities of liver and lung were associated with the fetal ascites in our case.

Our patient was the second child of a 23 year old white female, and the period of gestation was 37 weeks. The past history and prenatal course of the mother were noncontributory. The mother's blood type was A, Rh negative and the father's was A, Rh positive. Cord blood was O, Rh negative, Coombs test negative. Atypical antibodies could not be demonstrated in the mother's blood. Delivery by breech extraction was halted by the distended fetal abdomen; it was necessary to perform fetal abdominal paracentesis. Fetal heart sounds were audible just prior to the paracentesis; the infant was stillborn.

The placenta weighed 900 grams (normal about 400 grams); it was increased in diameter and about double the normal thickness. Microscopically the chorionic villi appeared bulky, edematous, immature, and irregularly congested. In the cord, one umbilical artery was markedly hypoplastic, with pinpoint lumen.

At necropsy the body was small (39 centimeters from crown to heel) and weighed 2350 grams. The peritoneal cavity was markedly distended (about 500 cubic centimeters of fluid had been removed by the paracentesis). Loops of small intestine were fused by chronic inflammation of the serosa, and the parietal peritoneum showed patches of chronic inflammatory thickening. The extrahepatic bile ducts and papilla of Vater were patent. The liver was markedly enlarged, icteric, and increased in consistency. On section, irregularly distributed areas of fibrosis were evident. Microscopically the lobular pattern was normal. The portal areas were markedly increased in width, due to the conversion of the peripheral portions of the lobules into a spongy fibrovascular tissue containing numerous tiny bile ducts. There were no evidences of nodular regeneration, inflammatory cell infiltrations, or parenchymal giant cells. The original portal tracts with their arteries, veins, and ducts could be clearly made out and appeared normal.

The heart was displaced to the left by a cystic lower lobe of the right lung. The displaced heart, in turn, compressed the left lung mediposteriorly. Within the cystic right lower lobe, a large branch of the right pulmonary artery communicated by direct arteriovenous continuity with a large, worm-like, anomalous pulmonary vein. The site of transition from artery to vein was abrupt and was marked by a thin, membranous, valve-like structure.

The lower lobe of the right lung was markedly enlarged. It contained one large cyst, 7 centimeters in diameter, and the remainder of the lobe was honeycombed by tiny cysts. The large cyst was filled with yellowish clear serous fluid. There were no gross evidences of direct communication of bronchi with the main cyst cavity. Microscopically this cyst was lined by ciliated columnar epithelium and terminal bronchioles opened directly into it.

The ascites is attributable to the combined effects of portal stasis associated with the structural malformation of the liver, and cardiac stasis transmitted directly to

the portal system by way of the ductus venosus. Right heart failure resulted from the extra load on the right side transmitted through the arteriovenous shunt; additional evidences of stasis were noted in the enlarged spleen, engorged intercostal and gastrointestinal vessels, and in the markedly congested hemorrhoidal veins with perineal hemorrhage.

The malformation of hepatic architecture corresponds to that described by Potter as cystic fibrosis of the liver[3]. It may be accompanied by cystic malformations in other organs[4]. A primary vascular abnormality in the liver has also been suggested[5].

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DISCUSSION

JOSEPH C. EHRLICH: One of the main problems in this case is the classification and pathogenesis of the structural changes in the liver. One may even question if the term cirrhosis is properly applied to these alterations except in the broadest sense, since there is no fundamental distortion of hepatic architecture. Because of the sharp delimitation of the anatomic changes to the paraportal zone of the hepatic lobules, one has to consider primary cholangiolitic, primary vascular, and primary peripheral hepatocellular changes as possible pathogenetic mechanisms. Sections of this liver were studied by several consultants. Their opinions were not in agreement. Dr. Edith Potter suggested the diagnosis of fibrocystic disease of the liver in a precystic stage. This form of cystic disease of the liver is usually associated with polycystic kidneys, or more rarely with cystic pancreas or cystic spleen. There were no cystic changes in any of these organs in our case. We have been unable to find a previous report of a case of combined cystic disease of liver and lung.

HANS POPPER: I was one of those who saw the slides of this case. I would agree with the diagnosis of a developmental defect rather than an inflammatory reaction of the character of cirrhosis. It is not a cystic type of malformation but can be rather compared with the microhamartomas or Meyenberg complexes except that, in the instance in question, considerable proliferation of venous and arterial vessels can be noted. It is known that in some cases of Meyenberg complexes portal hypertension is found. Most of them occur in children, but I know of one instance in an adult who bled to death from esophageal varices. I am not aware of ascites being reported, but in the specimen observed, the process seems to extend in places to the hepatic vein to produce a postsinusoidal component of portal hypertension, which is usually associated with ascites.

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SANITATION IN RAT CONTROL*

REPORT BY THE

COMMITTEE ON PUBLIC HEALTH**

THE NEW YORK ACADEMY OF MEDICINE

FOR some time the Committee on Public Health of The New York Academy of Medicine has been concerned about the reportedly large numbers of rats in New York City.

The Committee's concern has arisen out of the damage and danger that rats bring. Generally, the wild rat is an object of repugnance, an attitude which it has earned. It causes tremendous physical destruction. But aside from psychological and economic considerations, it is a menace to safety and health. It has an authentic reputation for biting persons, particularly infants. Just as dangerous is its ability to transmit disease. For these reasons, the Committee points to the desirability, indeed necessity, of a concentrated and sustained effort to rid New York City of its rats.

There are no accurate and reliable current figures on the number of rats in New York City. This lack of data is unfortunate because it leaves unknown the magnitude and distribution of this pest and thereby renders difficult the measurement of effectiveness of any exterminative program. The only available data which warrant the impression that rats are numerous in the city are the reports of rat bites. For the past five years in New York City these are:

1955	498
1956	582
1957	626
1958	566
1959	767

These figures are for reported rat bites and are unconfirmed. However, indirect as is this evidence on the prevalence of rats, it nevertheless supports the belief that they are present in large numbers.

Effective methods are known for reducing the rat population rapidly by extermination. But experience has shown that this measure alone brings only temporary relief, and that if additional procedures are not employed, the number of rats soon returns to its previous level. Ratproofing of dwellings is of course sensible and worthwhile. But in the opinion of the Committee, the most effective and important public health measure to keep down the level of rat population is to

*Report prepared by Subcommittee on Sanitation in Rat Control, comprised of: Frederick R. Bailey, M.D., Chairman; Henry Aranow, Jr., M.D.; Abram Blau, M.D.; Arthur A. Fischl, M.D.; Philip M. Stimson, M.D.; H. D. Kruse, M.D., Secretary.

**Authorized by the Committee on Public Health at its meeting on June 6, 1960.

deprive these animals of their food supply by preventing access to all edible material, including refuse. Simple as this approach seems, it is perhaps the most difficult of achievement in some segments of the population since it requires education in the formation of new habits. Nevertheless, although education in sanitation is a formidable undertaking, it is one of the most significant measures in rat reduction and it is achievable. It is a challenge with valuable rewards.

The Health Department has promised and embarked upon a vigorous program of rodent control. But by the very nature and magnitude of the task, the Department cannot accomplish the desired results unaided. It needs and deserves the active cooperation of every citizen.

The Committee on Public Health strongly supports an all-out campaign to rid the city of rats. Furthermore, it subscribes to the principle that if permanent reduction is to be achieved, an important and essential part of any campaign is education in simple sanitation, specifically keeping edible material from rats.

The Committee recommends that in any program or demonstration of rat control, the effectiveness of the particular approach should be measured as precisely as possible by close estimation of the before-and-after rat census.

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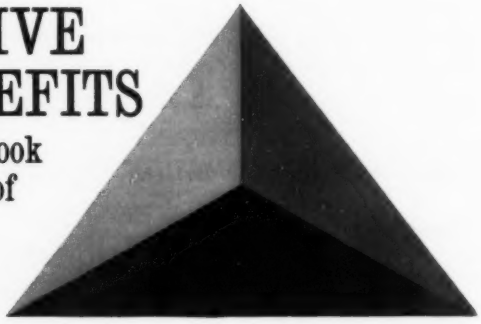

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Each capsule contains: Ethinyl Estradiol 0.01 mg. • Methyl Testosterone 2.5 mg. • d-Amphetamine Sulfate 2.5 mg. • Vitamin A (Acetate) 5,000 U.S.P. Units • Vitamin D 500 U.S.P. Units • Vitamin B_{12} with AUTRINIC® Intrinsic Factor Concentrate 1/15 U.S.P. Unit (Oral) • Thiamine Mononitrate (B_1) 5 mg. • Riboflavin (B_2) 5 mg. • Niacinamide 15 mg. • Pyridoxine HCl (B_6) 0.5 mg. • Calcium Pantothenate 5 mg. • Choline Bitartrate 25 mg. • Inositol 25 mg. • Ascorbic Acid (C) as Calcium Ascorbate 50 mg. • l-Lysine Monohydrochloride 25 mg. • Vitamin E (Tocopherol Acid Succinate) 10 Int. Units • Rutin 12.5 mg. • Ferrous Fumarate (Elemental iron, 10 mg.) 30.4 mg. • Iodine (as KI) 0.1 mg. • Calcium (as $CaHPO_4$) 35 mg. • Phosphorus (as $CaHPO_4$) 27 mg. • Fluorine (as CaF_2) 0.1 mg. • Copper (as CuO) 1 mg. • Potassium (as K_2SO_4) 5 mg. • Manganese (as MnO_2) 1 mg. • Zinc (as ZnO) 0.5 mg. • Magnesium (MgO) 1 mg. • Boron (as $Na_2B_4O_7.10H_2O$) 0.1 mg. Bottles of 100, 1000.

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

A New Major Medical Resource

ALDACTONE®

(Brand of Spironolactone)

For Relief of Intractable Edema

ALDACTONE is a new classic step forward in the treatment of severe and resistant edema, achieving hitherto unmatched efficacy in relieving this condition.

A typical case history illustrates the extent to which Aldactone can supplement and advance established medical resources for treating edema and ascites.

Report of a Case*

Mrs. L. S., 44, was admitted to the hospital on April 17, 1959, with massive ascites, 3-plus edema of the legs and moderate pulmonary congestion. Three previous admissions had established that she had rheumatic heart disease with cardiac enlargement, atrial fibrillation and mixed valvular lesions.

She was placed on a regimen of bed rest, digitalis and 0.5 Gm. of sodium daily. On treatment which included mercurials parenterally, hydrochlorothiazide, KCl, NH_4Cl, aminophylline, prednisone, acetazoleamide and lysine monochloride the patient lost 15 pounds, but her ascites did not diminish noticeably and her weight remained within the range of 130 to 135 pounds from May 1 to May 30.

On May 30, 100 mg. of Aldactone q.i.d. was added to her regimen. Progressive and continuous diuresis followed. Weight dropped from 130 to 107 pounds, her normal weight. The patient was discharged on June 14 completely free from ascites and peripheral edema.

She was maintained on digitalis and hydrochlorothiazide and had no further weight gain until December 1959. She was then given 400 mg. of Aldactone daily for five days and again achieved dry weight, which was maintained as of February 1960.

SUPPLIED: Aldactone (brand of spironolactone) is supplied as compression-coated yellow tablets of 100 mg.

*Klass, A.: Cur. Therap. Res. 2:322 (July) 1960.

G. D. SEARLE & CO., Chicago 80, Illinois
Research in the Service of Medicine

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Parkchester, Bronx *Jamaica, Queens*

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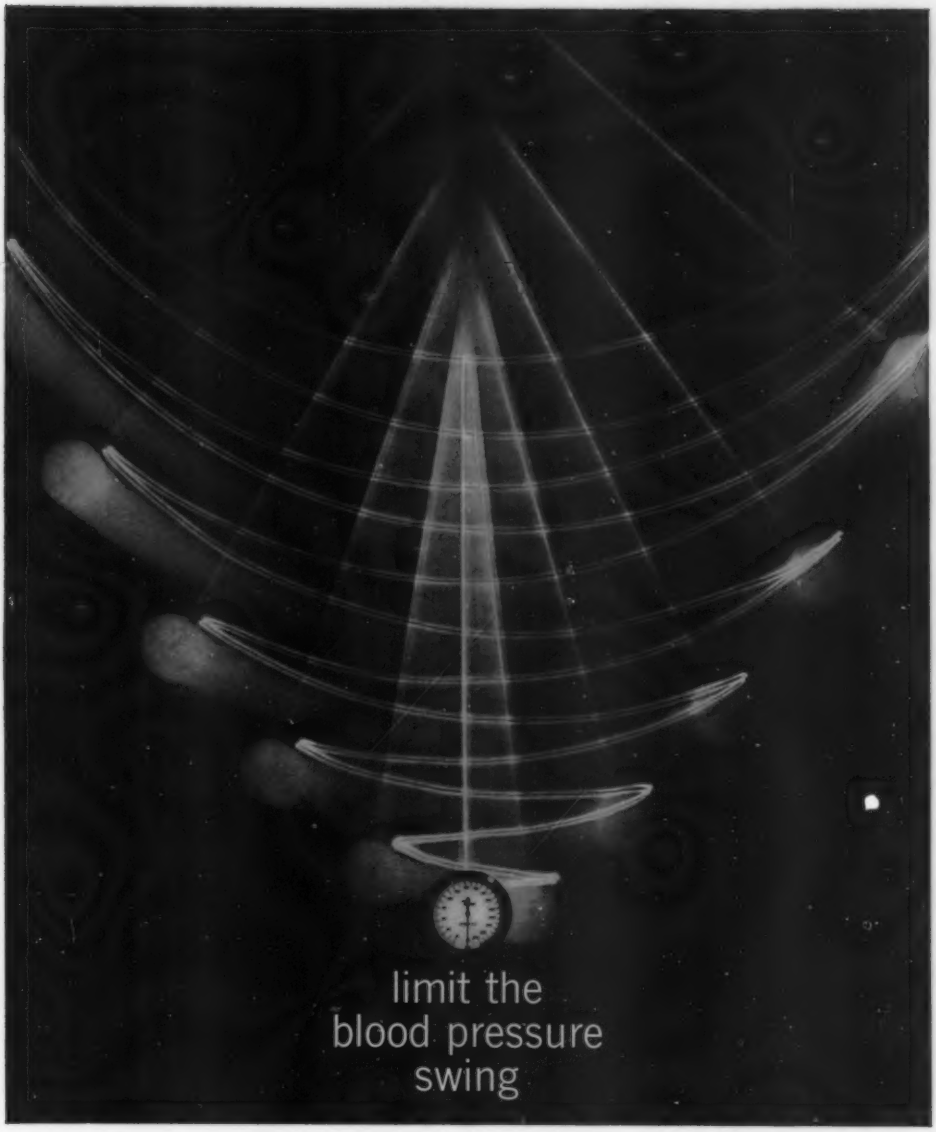

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Supply: Rautrax-N — capsule-shaped tablets — 50 mg. Raudixin, 4 mg. Naturetin, and 400 mg. potassium chloride. Rautrax-N Modified — capsule-shaped tablets — 50 mg. Raudixin, 2 mg. Naturetin, and 400 mg. potassium chloride. For complete information write Squibb, 745 Fifth Avenue, New York 22, N. Y.

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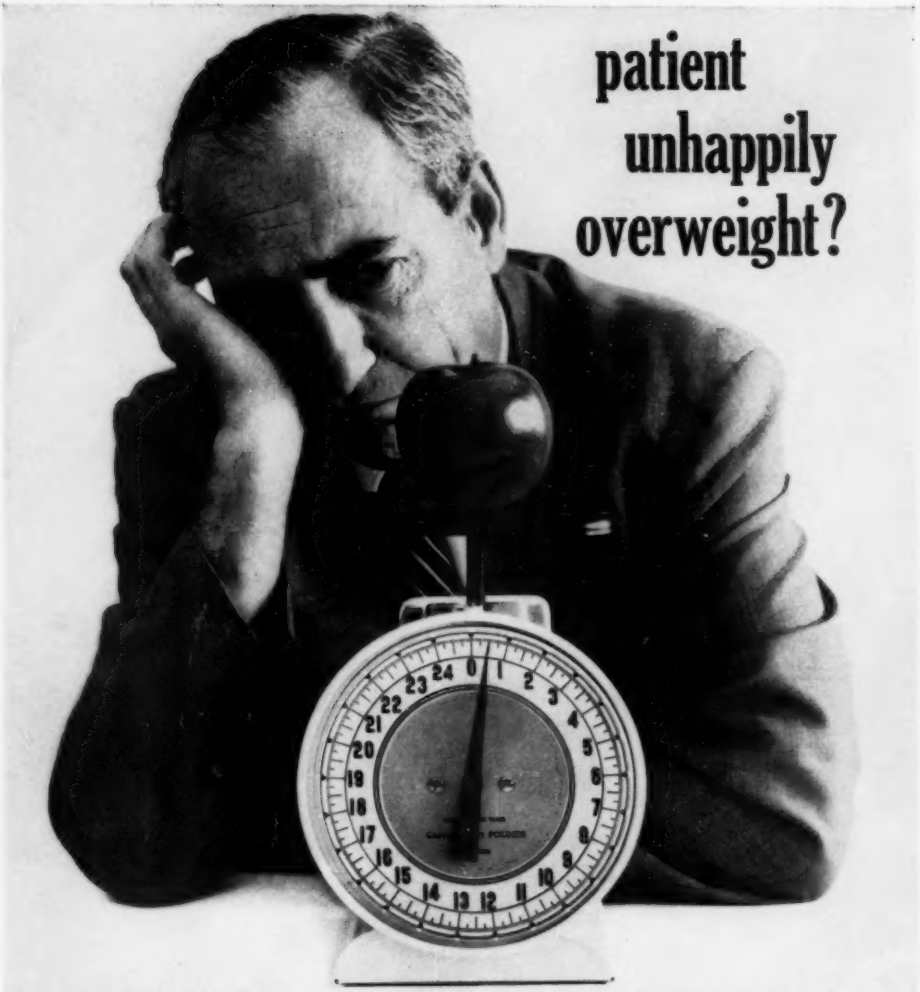

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Controls food craving, keeps the reducer happy—In obesity, "our drug of choice has been methedrine . . . because it produces the same central effect with about one-half the dose required with plain amphetamine, because the effect is more prolonged, and because undesirable peripheral effects are significantly minimized or entirely absent."[1] Literature available on request.

Supplied: Tablets 5 mg., scored. Bottles of 100 and 1000.

[1] Douglas, H. S.: West. J. Surg. 59:238 (May) 1951.

BURROUGHS WELLCOME & CO. (U. S. A.) INC., Tuckahoe, New York

Acts within minutes—KOAGAMIN, unlike other hemostatic agents, acts *quickly* in *minimal* dosages. Working on the late phases of the clotting mechanism, KOAGAMIN does not require massive and prolonged pre- or postoperative dosages to control capillary and venous bleeding.

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KOAGAMIN, an aqueous solution of oxalic (5 mg. per cc.) and malonic (2.5 mg. per cc.) acids for parenteral use, is supplied in 10-cc. diaphragm-stoppered vials.

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BEFORE, DURING AND AFTER SURGERY

KOAGAMIN®

(parenteral hemostat)

controls bleeding with minimal dosage and maximum safety

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AS A SERVICE TO THE PRESCRIBING PHYSICIAN, BELOW IS A COMPLETE STATEMENT OF DOSAGE AND PRECAUTIONS AS SET FORTH IN THE BASIC PRODUCT LITERATURE.

DOSAGE (Tablets and Suspension)

For severe infections:

Adults: 4 tablets or 8 teaspoonfuls (2 Gm) initially (followed by 2 tablets or 4 teaspoonfuls (1 Gm) daily thereafter.

Children:

Body Weight	Initial Dose	Daily Dose Every 24 Hours Thereafter
20 lbs	0.5 Gm 1 tablet* or 2 teaspoonfuls	0.25 Gm ½ tablet or 1 teaspoonful
40 lbs	1 Gm 2 tablets or 4 teaspoonfuls	0.5 Gm 1 tablet or 2 teaspoonfuls
80 lbs	2 Gm 4 tablets or 8 teaspoonfuls	1 Gm 2 tablets or 4 teaspoonfuls

DOSAGE (Pediatric Drops)

For neonate to severe infections: 2 drops (25 mg) per pound body weight followed by 1 drop (12.5 mg) per pound body weight daily thereafter.

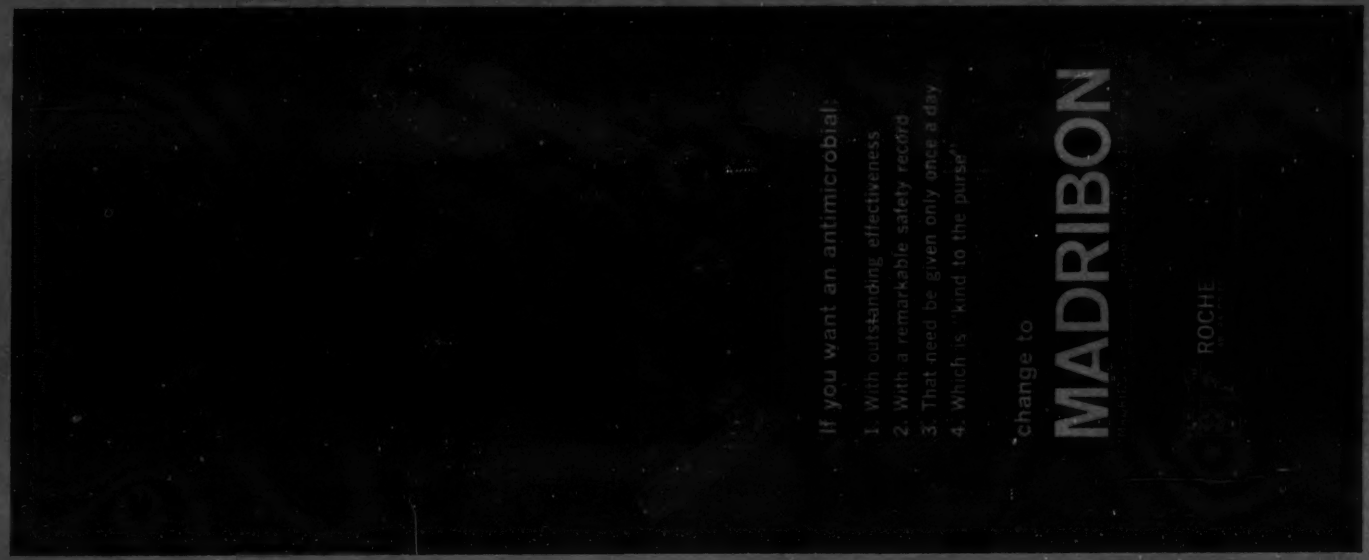
Continue therapy for 5 to 7 days or until patient is asymptomatic for at least 48 hours.

For mild infections: Less severe infections will usually respond to one-half the above dosage.

Caution: The usual precautions in sulfonamide therapy should be observed, including the maintenance of an adequate fluid intake. In the event of headache, nausea, vomiting, urticaria, rash, fever or hematuria, the use of the drug should be discontinued. When Madribon is used intermittently or for prolonged periods, blood counts should be performed to determine whether blood dyscrasias have occurred. The use of the drug should be stopped immediately if alterations in the hematopoietic system are observed. Patients with impaired renal function should be followed closely since renal impairment may cause excessive drug accumulation. Madribon should not be administered to patients with a history of adverse reactions to sulfonamide therapy.

Madribon, like most sulfonamides and certain other drugs, is probably contraindicated in premature infants—and newborn infants for the first week of life—because of underdeveloped enzyme systems and immature liver and renal functions.

Packages: Madribon Tablets: 0.5 Gm, double-scored, monogrammed, gold colored—bottles of 30, 100, 250, and 1000. Madribon Suspension: 0.25 Gm/teasp. (5 cc), custard flavored—bottles of 4 oz and 16 oz. Madribon Pediatric Drops: 250 mg/cc (20 drops)—10-cc bottle with drop-dispensing tip.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